PYRIMIDINE COMPOUNDS FOR THE TREATMENT OF INFLAMMATION

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 60/513,770, filed October 23, 2003, the contents of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] This invention generally relates to anti-inflammatory pharmaceutical agents and specifically relates to pyrimidine compounds as inhibitors of IKK-2, an IκB kinase. The invention is further related to compositions comprising such compounds, and methods for treating cancer, inflammation, and inflammation-associated disorders such as arthritis.

BACKGROUND OF THE INVENTION

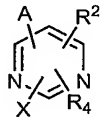
[0003] Rheumatoid arthritis is a common inflammatory disease affecting approximately 1% of the population. The disease is characterized by multiple painful swollen joints that severely limit the patient's daily function, and can progress to the destruction of the affected joints. A common treatment for rheumatoid arthritis is anti-inflammatory steroids. Steroids are clinically very effective, but are limited in their use because of multiple severe side-effects. Thus, a need exists for an anti- rheumatoid arthritis treatment that offers the potency of steroids without the associated toxicity. One of the mechanisms by which steroids exert their broad spectrum anti-inflammatory action is by inhibiting the activation of the transcription factor NF-κB. NF-κB plays a prominent role in immune and inflammatory responses by regulating the transcription of many early, inducible genes in a variety of cells including inflammatory enzymes such as COX-2 and iNOS. NF-κB is sequestered in an inactive form in the cytoplasm by a member of the IκB family of inhibitory

proteins, and this prevents gene transcription of these responsive genes in the nucleus. Stimulation of cells leads to the phosphorylation, ubiquination and degradation of IκB thereby releasing NF-κB to the nucleus for activation of gene transcription. Chronic activation of NF-κB has been demonstrated in vascular endothelium and synovial lining cells from patients with RA. Recently the IκB kinases (IKK-1 and IKK-2), which phosphorylate IκB and thereby initiate its degradation, have been cloned and initially characterized; these kinases appear to represent the critical, common denominator in the activation of NF-κB since antisense or dominant-negative IKK constructs block NF-κB nuclear translocation and inhibit NF-κB linked reported genes. Therefore, IKK-1 and/or IKK-2 represent novel and powerful targets for drug development.

[0004] It has been reported that selective IKK-2 inhibitors could be useful for the treatment of inflammatory diseases. See, e.g., Karin et al., Nat. Revs. **3**, 17-26, 2004.

SUMMARY OF THE INVENTION

[0005] This invention provides for, in part, IKK-2-inhibiting compounds of Formula I:

[0006]  I

[0007] wherein X is aryl substituted by R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e};

[0008] wherein A is selected from the group consisting of cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl, and heteroaryl, wherein A is optionally substituted by one or more substituents independently selected from the group consisting of R^3;

[0009] wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, and R^3 are independently selected from the group consisting of hydrido, cyano, hydroxyl, nitro, halo, alkyl, haloalkyl, hydroxyalkyl, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl,

haloalkoxy, aryl, alkenyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, acylamino, $-OR^{10}$, $-SR^{7a}$, $-SO_2N(R^{7a})R^{7b}$, $-NR^{8a}R^{8b}$, $-NR^{8a}COR^{8c}$, $-NR^{8a}CO(OR^{8c})$, $-NR^{8a}SO_2R^{9a}$, $-NR^{8a}SO_2N(R^{9a})R^{9b}$, $-NR^{8a}CON(R^{9a})R^{9b}$, $-COR^{8a}$, $-CO_2R^{7a}$, and $-CON(R^{7a})R^{7b}$, wherein said aryl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, or alkenyl may be substituted with one or more substituents selected from the group consisting of R^{8a};

[0010] wherein R^2 is $-NR^{11a}R^{11b}$;

[0011] wherein R^4 is selected from the group consisting of cyano, $-CO_2R^{5a}$, and $-CH_2OR^{5a}$, $CONR^{5a}R^{5b}$;

[0012] wherein R^{5a}, R^{5b}, and R^6 are independently selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl;

[0013] wherein R^{7a} and R^{7b} are independently selected from the group consisting of hydrido, aryl, heteroaryl, aralkyl, heterocycloalkyl, heterocycloalkenyl, haloalkyl, aralkylamino, alkylaminoalkyl, N,N-dialkylaminoacyl, alkyl, alkenyl, alkynyl, and heteroaralkyl;

[0014] wherein R^{8a} and R^{8b} are independently selected from the group consisting of hydrido, alkyl, aryl, heteroaryl, aralkyl, heterocycloalkyl, heterocycloalkenyl, cycloalkyl, haloalkyl, aralkylamino, amino, aminoalkyl, aminoacyl, and heteroaralkyl, wherein said alkyl, aryl, heteroaryl, aminoalkyl, or aralkyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate, isothiocyanate, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylamino, alkylsulfonamido, aminoalkyl, alkylaminoalkyl, alkoxy, halo, acyloxy, haloalkyl, haloalkoxy, acyl, hydroxyalkoxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, alkyldioxy, hydroxyalkyl, N-alkylamino, alkoxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, N,N-dialkylaminoalkoxy, heterocycloalkyl, heterocycloalkenyl, and heteroaryl, wherein said heterocycloalkyl,

heterocycloalkenyl, or heteroaryl substituents may be substituted with a substituent selected from the group consisting of alkyl, N-alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

[0015] wherein R^{8c} is selected from the group consisting of hydrido, nitro, azido, alkyl, aryl, heteroaryl, aralkyl, heterocycloalkyl, heterocycloalkenyl, cycloalkyl, haloalkyl, aralkylamino, amino, aminoalkyl, aminoacyl, and heteroaralkyl, wherein said alkyl, aryl, heteroaryl, aminoalkyl, or aralkyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate, isothiocyanate, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylamino, alkylsulfonamido, aminoalkyl, alkylaminoalkyl, alkoxy, halo, acyloxy, haloalkyl, haloalkoxy, acyl, hydroxyalkoxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, alkyldioxy, hydroxyalkyl, N-alkylamino, alkoxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, N,N-dialkylaminoalkoxy, heterocycloalkyl, heterocycloalkenyl, and heteroaryl, wherein said heterocycloalkyl, heterocycloalkenyl, or heteroaryl substituents may be substituted with a substituent selected from the group consisting of alkyl, N-alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

[0016] wherein R^{9a} and R^{9b} are independently selected from the group consisting of hydrido, alkyl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, haloalkyl, aralkylamino, heteroaralkyl, aryl, and aralkyl, wherein said aryl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, or aralkyl moieties may be substituted with one or more radicals selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkoxy, phenoxy, benzyloxy, N,N-dialkylaminoalkoxy, heteroaryl, heterocycloalkyl, and heterocycloalkenyl;

[0017] wherein R^{10} is selected from the group consisting of hydrido, aryl, heteroaryl, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl,

alkylaminoalkyl, alkoxyalkyl, heterocycloalkyl, heteroaryl, and heterocycloalkenyl;

[0018] wherein R^{11a} and R^{11b} are independently selected from the group consisting of hydrido, aryl, heteroaryl, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocycloalkyl, heteroaryl, and heterocycloalkenyl;

[0019] wherein R^2 and R^4 may form a 4- to 6-membered heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting of S, SO, SO_2, O, N, and NR^6;

[0020] wherein R^{7a} and R^{7b} may be taken together to form a 3- to 7-membered heterocyclic moiety having 1 to 3 heteroatoms selected from the group consisting of S, SO, SO_2, O, N, and NR^{8a}; and

[0021] wherein R^{9a} and R^{9b} may be taken together to form a 3- to 7-membered heterocyclic moiety having 1 to 3 heteroatoms selected from the group consisting of S, SO, SO_2, O, N, and NR^{8a};

[0022] or a pharmaceutically acceptable salt thereof.

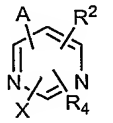
[0023] The instant invention is also directed to pharmaceutical compositions comprising a compound of Formula I or a pharmaceutically-acceptable salt thereof, as defined above, and a pharmaceutically acceptable carrier, diluent, or adjuvant.

[0024] The instant invention is also directed to a method of treating or preventing inflammation or an inflammation-associated disorder, the method comprising administering a compound of Formula I or a pharmaceutically acceptable salt thereof to a subject in need of such treatment or susceptible to such inflammation or inflammation-associated disorder.

[0025] Other objects of the invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0026] In accordance with the present invention, Applicants have discovered a class of IKK-2-inhibiting compounds of Formula I:

[0027]  I

[0028] wherein X is aryl substituted by R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e};

[0029] wherein A is selected from the group consisting of cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl, and heteroaryl, wherein A is optionally substituted by one or more substituents independently selected from the group consisting of R^3;

[0030] wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, and R^3 are independently selected from the group consisting of hydrido, cyano, hydroxyl, nitro, halo, alkyl, haloalkyl, hydroxyalkyl, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, haloalkoxy, aryl, alkenyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, acylamino, $-OR^{10}$, $-SR^{7a}$, $-SO_2N(R^{7a})R^{7b}$, $-NR^{8a}R^{8b}$, $-NR^{8a}COR^{8c}$, $-NR^{8a}CO(OR^{8c})$, $-NR^{8a}SO_2R^{9a}$, $-NR^{8a}SO_2N(R^{9a})R^{9b}$, $-NR^{8a}CON(R^{9a})R^{9b}$, $-COR^{8a}$, $-CO_2R^{7a}$, and $-CON(R^{7a})R^{7b}$, wherein said aryl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, or alkenyl may be substituted with one or more substituents selected from the group consisting of R^{8a};

[0031] wherein R^2 is $-NR^{11a}R^{11b}$;

[0032] wherein R^4 is selected from the group consisting of cyano, $-CO_2R^{5a}$, and $-CH_2OR^{5a}$, $CONR^{5a}R^{5b}$;

[0033] wherein R^{5a}, R^{5b}, and R^6 are independently selected from the group consisting of hydrido, hydroxyl, alkoxy, alkyl, haloalkyl, aryl, and heteroaryl;

[0034] wherein R^{7a} and R^{7b} are independently selected from the group consisting of hydrido, aryl, heteroaryl, aralkyl, heterocycloalkyl, heterocycloalkenyl, haloalkyl, aralkylamino, alkylaminoalkyl, N,N-dialkylaminoacyl, alkyl, alkenyl, alkynyl, and heteroaralkyl;

[0035] wherein R^{8a} and R^{8b} are independently selected from the group consisting of hydrido, alkyl, aryl, heteroaryl, aralkyl, heterocycloalkyl, heterocycloalkenyl, cycloalkyl, haloalkyl, aralkylamino, amino, aminoalkyl, aminoacyl, and heteroaralkyl, wherein said alkyl, aryl, heteroaryl, aminoalkyl, or aralkyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate, isothiocyanate, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylamino, alkylsulfonamido, aminoalkyl, alkylaminoalkyl, alkoxy, halo, acyloxy, haloalkyl, haloalkoxy, acyl, hydroxyalkoxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, alkyldioxy, hydroxyalkyl, N-alkylamino, alkoxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, N,N-dialkylaminoalkoxy, heterocycloalkyl, heterocycloalkenyl, and heteroaryl, wherein said heterocycloalkyl, heterocycloalkenyl, or heteroaryl substituents may be substituted with a substituent selected from the group consisting of alkyl, N-alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

[0036] wherein R^{8c} is selected from the group consisting of hydrido, nitro, azido, alkyl, aryl, heteroaryl, aralkyl, heterocycloalkyl, heterocycloalkenyl, cycloalkyl, haloalkyl, aralkylamino, amino, aminoalkyl, aminoacyl, and heteroaralkyl, wherein said alkyl, aryl, heteroaryl, aminoalkyl, or aralkyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate, isothiocyanate, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylamino, alkylsulfonamido, aminoalkyl, alkylaminoalkyl, alkoxy, halo, acyloxy, haloalkyl, haloalkoxy, acyl, hydroxyalkoxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, alkyldioxy, hydroxyalkyl, N-alkylamino, alkoxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, N,N-dialkylaminoalkoxy, heterocycloalkyl, heterocycloalkenyl, and heteroaryl, wherein said heterocycloalkyl, heterocycloalkenyl, or heteroaryl

substituents may be substituted with a substituent selected from the group consisting of alkyl, N-alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

[0037] wherein R^{9a} and R^{9b} are independently selected from the group consisting of hydrido, alkyl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, haloalkyl, aralkylamino, heteroaralkyl, aryl, and aralkyl, wherein said aryl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, or aralkyl moieties may be substituted with one or more radicals selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkoxy, phenoxy, benzyloxy, N,N-dialkylaminoalkoxy, heteroaryl, heterocycloalkyl, and heterocycloalkenyl;

[0038] wherein R^{10} is selected from the group consisting of hydrido, aryl, heteroaryl, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxyalkyl, heterocycloalkyl, heteroaryl, and heterocycloalkenyl;

[0039] wherein R^{11a} and R^{11b} are independently selected from the group consisting of hydrido, aryl, heteroaryl, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocycloalkyl, heteroaryl, and heterocycloalkenyl;

[0040] wherein R^2 and R^4 may form a 4- to 6-membered heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting of S, SO, SO_2, O, N, and NR^6;

[0041] wherein R^{7a} and R^{7b} may be taken together to form a 3- to 7-membered heterocyclic moiety having 1 to 3 heteroatoms selected from the group consisting of S, SO, SO_2, O, N, and NR^{8a}; and

[0042] wherein R^{9a} and R^{9b} may be taken together to form a 3- to 7-membered heterocyclic moiety having 1 to 3 heteroatoms selected from the group consisting of S, SO, SO_2, O, N, and NR^{8a};

[0043] or a pharmaceutically acceptable salt thereof.

[0044] Compounds of Formula I may be useful for treating, among other things, inflammation in a subject, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of the present invention may be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, acute rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, and pyogenic arthritis.

[0045] Compounds of the invention may be further useful in the treatment of frailty, asthma, chronic obstructive pulmonary disease (COPD), bronchitis, menstrual cramps (e.g., dysmenorrhea), premature labor, tendinitis, bursitis, dermatological conditions such as psoriasis, eczema, burns, sunburn, dermatitis, pancreatitis, hepatitis, and from post-operative inflammation including from ophthalmic surgery such as cataract surgery and refractive surgery. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. Compounds of the invention would be useful for the prevention or treatment of cancer, such as colorectal cancer, and cancer of the breast, lung, prostate, bladder, cervix and skin, as well as treatment of cancer stem cells. Compounds of the invention would be useful in treating inflammation and tissue damage in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like.

[0046] The compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compounds would also be useful for the treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, and central nervous system damage resulting from stroke, ischemia and trauma. The compounds of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compounds would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, and atherosclerosis. The compounds would also be useful in the treatment of pain, but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer. The compounds would be useful for the prevention of dementias, such as Alzheimer's disease.

[0047] Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

[0048] The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatory therapies, such as together with steroids, NSAIDs, COX-2 selective inhibitors, 5-lipoxygenase inhibitors, LTB_4 antagonists and LTA_4 hydrolase inhibitors.

[0049] Other conditions in which the compounds of the present invention may provide an advantage include cardiovascular ischemia, diabetes (type I or type II), congestive heart failure, myocarditis, atherosclerosis, migraine, glaucoma, aortic aneurysm, reflux esophagitis, diarrhea, irritable bowel syndrome, cystic fibrosis, emphysema, asthma, bronchiectasis, hyperalgesia (allodynia), and cerebral ischemia (both focal ischemia, thrombotic stroke and global ischemia (for example, secondary to cardiac arrest).

[0050] The compounds of the present invention may also be useful in the treatment of pain including somatogenic (either nociceptive or neuropathic), both acute and chronic. A compound of the present invention could be used in any situation including neuropathic pain that a common NSAID or opioid analgesic would traditionally be administered.

[0051] Conjunctive treatment of a compound of the present invention with an antineoplastic agent may produce a beneficial effect or alternatively reduce the toxic side effects associated with chemotherapy by reducing the therapeutic dose of the side effect-causing agent needed for therapeutic efficacy or by directly reducing symptoms of toxic side effects caused by the side effect-causing agent. A compound of the present invention may further be useful as an adjunct to radiation therapy to reduce side effects or enhance efficacy. In the present invention, another agent which can be combined therapeutically with a compound of the present invention includes any therapeutic agent which is capable of inhibiting the enzyme cyclooxygenase-2 ("COX-2"). Preferably such COX-2 inhibiting agents inhibit COX-2 selectively relative to the enzyme cyclooxygenase-1 ("COX-1"). Such a COX-2 inhibitor is known as a "COX-2 selective inhibitor". More preferably, a compound of the present invention can be therapeutically combined with a COX-2 selective inhibitor wherein the COX-2 selective inhibitor selectively inhibits COX-2 at a ratio of at least 10:1 relative to inhibition of COX-1, more preferably at least 30:1, and still more preferably at least 50:1 in an *in vitro* test. COX-2 selective inhibitors useful in therapeutic combination with the compounds of the present invention include celecoxib, valdecoxib, deracoxib, etoricoxib, rofecoxib, ABT-963 (2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl-3(2H)-pyridazinone; described in PCT Publication No. WO 00/24719), or meloxicam. A compound of the present invention can also be advantageously used in therapeutic combination with a prodrug of a COX-2 selective inhibitor, for example parecoxib.

[0052] Another chemotherapeutic agent which may be useful in combination with a compound of the present invention can be selected, for example, from the following non-comprehensive and non-limiting list: Alpha-difluoromethylornithine (DFMO), 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrill Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, tyrosine protein kinase inhibitors, Taiho UFT, uricytin, Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromus-tine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin, trimelamol, Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont

ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calichemycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindamycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 zorubicin, alpha-carotene, alpha-difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphethinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristo-Myers BMY-40481, Vestar boron-10, bromofosfamide,

Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemex CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, elliprabin, elliptinium acetate, Tsumura EPMTC, ergotamine, etoposide, etretinate, fenretinide, Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, Otsuak K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, merbarone, merocyanine derivatives, methylanilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoquidone, mopidamol, motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids, Nisshin Flour Milling N-021, N-acylated-dehydroalanines, nafazatrom, Taisho NCU-190, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, octreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm

SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides, Yamanouchi YM-534, uroguanylin, combretastatin, dolastatin, idarubicin, epirubicin, estramustine, cyclophosphamide, 9-amino-2-(S)-camptothecin, topotecan, irinotecan (Camptosar), exemestane, decapeptyl (tryptorelin), or an omega-3 fatty acid.

[0053] Examples of radioprotective agents which may be used in a combination therapy with the compounds of this invention include AD-5, adchnon, amifostine analogues, detox, dimesna, I-102, MM-159, N-acylated-dehydroalanines, TGF-Genentech, tiprotimod, amifostine, WR-151327, FUT-187, ketoprofen transdermal, nabumetone, superoxide dismutase (Chiron) and superoxide dismutase Enzon.

[0054] The compounds of the present invention may also be useful in treatment or prevention of angiogenesis-related disorders or conditions, for example, tumor growth, metastasis, macular degeneration, and atherosclerosis.

[0055] In a further embodiment, the present invention also provides therapeutic combinations for the treatment or prevention of ophthalmic disorders or conditions such as glaucoma. For example the present inventive compounds advantageously may be used in therapeutic combination with a drug which reduces the intraocular pressure of patients afflicted with glaucoma. Such intraocular pressure-reducing drugs include without limitation latanoprost, travoprost, bimatoprost, or unoprostol. The therapeutic combination of a compound of the present invention plus an intraocular pressure-reducing drug

may be useful because each is believed to achieve its effects by affecting a different mechanism.

[0056] In another combination of the present invention, the present inventive compounds can be used in therapeutic combination with an antihyperlipidemic or cholesterol-lowering drug such as a benzothiepine or a benzothiazepine antihyperlipidemic drug. Examples of benzothiepine antihyperlipidemic drugs useful in the present inventive therapeutic combination can be found in U.S. Patent No. 5,994,391, herein incorporated by reference. Some benzothiazepine antihyperlipidemic drugs are described in PCT Publication No. WO 93/16055. Alternatively, the antihyperlipidemic or cholesterol-lowering drug useful in combination with a compound of the present invention can be an HMG Co-A reductase inhibitor. Examples of HMG Co-A reductase inhibitors useful in the present therapeutic combination include, individually, benfluorex, fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, ZD-9720 (described in PCT Publication No. WO 97/06802), ZD-4522 (CAS No. 147098-20-2 for the calcium salt; CAS No. 147098-18-8 for the sodium salt; described in European Patent No. EP 521471), BMS 180431 (CAS No. 129829-03-4), or NK-104 (CAS No. 141750-63-2). The therapeutic combination of a compound of the present invention plus an antihyperlipidemic or cholesterol-lowering drug may be useful, for example, in reducing the risk of formation of atherosclerotic lesions in blood vessels. For example, atherosclerotic lesions often initiate at inflamed sites in blood vessels. It is established that antihyperlipidemic or cholesterol-lowering drug reduce risk of formation of atherosclerotic lesions by lowering lipid levels in blood. Without limiting the invention to a single mechanism of action, it is believed that one way the compounds of the present combination may work in concert to provide improved control of atherosclerotic lesions by, for example, reducing inflammation of the blood vessels in concert with lowering blood lipid levels.

[0057] In another embodiment of the invention, the present compounds can be used in combination with other compounds or therapies for the treatment of central nervous conditions or disorders such as migraine. For example, the present compounds can be used in therapeutic combination with caffeine, a 5-HT-1B/1D agonist (for example, a triptan such as sumatriptan, naratriptan, zolmitriptan, rizatriptan, almotriptan, or frovatriptan), a dopamine D4 antagonist (e.g., sonepiprazole), aspirin, acetaminophen, ibuprofen, indomethacin, naproxen sodium, isometheptene, dichloralphenazone, butalbital, an ergot alkaloid (e.g., ergotamine, dihydroergotamine, bromocriptine, ergonovine, or methyl ergonovine), a tricyclic antidepressant (e.g., amitriptyline or nortriptyline), a serotonergic antagonist (e.g., methysergide or cyproheptadine), a beta-andrenergic antagonist (e.g., propranolol, timolol, atenolol, nadolol, or metprolol), or a monoamine oxidase inhibitor (e.g., phenylzine or isocarboxazid).

[0058] The present invention includes compounds that selectively inhibit IKK-2 over other kinases. Such other kinases include, but are not limited to, Abl(h), Abl(T315I), Abl(T315I), AMPK, Aurora-A, BTK, CaMKII, CaMKIV, CDK1/cyclinB, CDK2, CDK2/cyclin A, CDK2/cyclinE, CHK1, CHK2, CK1, CK1(y), CK1δ, CK2, c-RAF(h), CSK, cSRC(h), DYRK1a, ERK2, Fyn, GSK3ß, IGF-1R, IKK1, IKKi, IKK2(h), JNK/SAPK1c, JNK1, JNK1α1(h), JNK2, JNK2α2(h), JNK3, Lck, MAPK1(h), MAPK2(h), MAPK2/ERK2, MAPKAP-K1a, MAPKAP-K2, MEK1, MK-2, MK-3, MKK1, MKK4, MKK6, MKK7, MKK7ß(h), MNK, MRSK2/APKAPk1b, MSK, MSK1, NEK2a, NEK6, p38 alpha, p38 beta, p38 delta, p38 gamma, p70 S6K, PAK2, PDGFRß, PDK1, PHK, PKA, PKBΔph, PKCζ, PKCα, PKCγ, PKCδ, PKCε, PRAK, ROCK-II, Rsk1, Rsk2, RSKB, SAPK2a/p38, SAPK2b, SAPK2b/p38ß2, SAPK3, SAPK3/p38g, SAPK4, SAPK4/p38d, SGK, TBK-1, and ZAP-70. The compounds may have an IKK-2 IC_{50} of less than about 10 μM, preferably less than about 1 μM, and have a selectivity ratio of IKK-2 inhibition over IKK-1 inhibition of at least 50, or at least

100. The compounds may have an IKK-1 IC_{50} of greater than 10 μM, or greater than 100 μM.

[0059] In one preferred embodiment, the compound of Formula I is a compound wherein X is C_{5-12} aryl substituted by R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e};

[0060] wherein A is selected from the group consisting of C_{3-12} cycloalkyl, C_{3-12} cycloalkenyl, C_{5-12} aryl, 5- to 12-membered heterocycloalkyl, 5- to 12-membered heterocycloalkenyl, and 5- to 12-membered heteroaryl, wherein A is optionally substituted by one or more substituents independently selected from the group consisting of R^3;

[0061] wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, and R^3 are independently selected from the group consisting of hydrido, cyano, hydroxyl, nitro, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{2-7} alkoxycarbonyl, C_{1-6} haloalkoxy, C_{5-12} aryl, C_{2-6} alkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, 5- to 12-membered heteroaryl, C_{2-10} acylamino, $-OR^{10}$, $-SR^{7a}$, $-SO_2N(R^{7a})R^{7b}$, $-NR^{8a}R^{8b}$, $-NR^{8a}COR^{8c}$, $-NR^{8a}CO(OR^{8c})$, $-NR^{8a}SO_2R^{9a}$, $-NR^{8a}SO_2N(R^{9a})R^{9b}$, $-NR^{8a}CON(R^{9a})R^{9b}$, $-COR^{8a}$, $-CO_2R^{7a}$, and $-CON(R^{7a})R^{7b}$, wherein said aryl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, or alkenyl moiety may be substituted with one or more substituents selected from the group consisting of R^{8a};

[0062] wherein R^4 is selected from the group consisting of cyano, $-CO_2R^{5a}$, and $-CH_2OR^{5a}$, $CONR^{5a}R^{5b}$;

[0063] wherein R^{5a}, R^{5b}, and R^6 are independently selected from the group consisting of hydrido, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{5-12} aryl, and 5- to 12-membered heteroaryl;

[0064] wherein R^{7a} and R^{7b} are independently selected from the group consisting of hydrido, C_{5-12} aryl, 5- to 12-membered heteroaryl, C_{4-18} aralkyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_{1-6} haloalkyl, C_{4-18} aralkylamino, C_{2-12} alkylaminoalkyl, N-N-di(C_{1-6} alkyl)amino(C_{1-6} alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and 4- to 18-membered heteroaralkyl;

[0065] wherein R^{8a} and R^{8b} are independently selected from the group consisting of hydrido, C_{1-6} alkyl, C_{5-12} aryl, 5- to 12-membered heteroaryl, C_{4-18} aralkyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_{3-12} cycloalkyl, C_{1-6} haloalkyl, C_{4-18} aralkylamino, amino, C_{1-6} aminoalkyl, C_{2-10} aminoacyl, and 4- to 18-membered heteroaralkyl, wherein said alkyl, aryl, heteroaryl, aminoalkyl, or aralkyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate, isothiocyanate, C_{1-6} alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, N-(C_{1-6} alkyl)amino, C_{1-6} alkylsulfonamido, C_{1-6} aminoalkyl, C_{2-12} alkylaminoalkyl, C_{1-6} alkoxy, halo, C_{2-10} acyloxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-10} acyl, C_{1-6} hydroxyalkoxy, N,N-di(C_{1-6} alkyl)amino(C_{2-10} acyl), C_{1-6} thioalkyl, C_{2-10} aminoacyloxy, C_{1-6} alkyldioxy, C_{1-6} hydroxyalkyl, N-(C_{1-6} alkyl)amino, C_{2-7} alkoxycarbonyl, C_{2-12} alkoxyalkyl, C_{2-6} alkenylamino, C_{2-6} alkynylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, N,N-di(C_{1-6} alkyl)amino(C_{1-6} alkoxy), 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, and 5- to 12-membered heteroaryl, wherein said 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, or 5- to 12-membered heteroaryl moiety may be substituted with a substituent selected from the group consisting of C_{1-6} alkyl, N-(C_{1-6} alkyl)amino, C_{1-6} aminoalkyl, C_{1-6} hydroxyalkyl, and C_{2-12} alkylaminoalkyl;

[0066] wherein R^{8c} is selected from the group consisting of hydrido, nitro, azido, C_{1-6} alkyl, C_{5-12} aryl, 5- to 12-membered heteroaryl, C_{4-18} aralkyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_{3-12} cycloalkyl, C_{1-6} haloalkyl, C_{4-18} aralkylamino, amino, C_{1-6} aminoalkyl, C_{2-10} aminoacyl, and 4- to 18-membered heteroaralkyl, wherein said alkyl, aryl, heteroaryl, aminoalkyl, or aralkyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate,

isothiocyanate, C_{1-6} alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, N-(C_{1-6} alkyl)amino, C_{1-6} alkylsulfonamido, C_{1-6} aminoalkyl, C_{2-12} alkylaminoalkyl, C_{1-6} alkoxy, halo, C_{2-10} acyloxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-10} acyl, C_{1-6} hydroxyalkoxy, N,N-di(C_{1-6} alkyl)amino(C_{2-10} acyl), C_{1-6} thioalkyl, C_{2-10} aminoacyloxy, C_{1-6} alkyldioxy, C_{1-6} hydroxyalkyl, N-(C_{1-6} alkyl)amino, C_{2-7} alkoxycarbonyl, C_{2-12} alkoxyalkyl, C_{2-6} alkenylamino, C_{2-6} alkynylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, N,N-di(C_{1-6} alkyl)amino(C_{1-6} alkoxy), 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, and 5- to 12-membered heteroaryl, wherein said 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, or 5- to 12-membered heteroaryl moiety may be substituted with a substituent selected from the group consisting of C_{1-6} alkyl, N-(C_{1-6} alkyl)amino, C_{1-6} aminoalkyl, C_{1-6} hydroxyalkyl, and C_{2-12} alkylaminoalkyl;

[0067] wherein R^{9a} and R^{9b} are independently selected from the group consisting of hydrido, C_{1-6} alkyl, 5- to 12-membered heteroaryl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_{1-6} haloalkyl, C_{4-18} aralkylamino, 4- to 18-membered heteroaralkyl, C_{5-12} aryl, and C_{4-18} aralkyl, wherein said aryl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, or aralkyl moiety may be substituted with one or more radicals selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, halo, C_{1-6} haloalkyl, cyano, C_{1-6} haloalkoxy, C_{2-10} acyl, carboxyl, hydroxy, C_{1-6} hydroxyalkoxy, phenoxy, benzyloxy, N,N-di(C_{1-6} alkyl)amino(C_{1-6} alkoxy), 5- to 12-membered heteroaryl, 3- to 12-membered heterocycloalkyl, and 3- to 12-membered heterocycloalkenyl;

[0068] wherein R^{10} is selected from the group consisting of hydrido, C_{5-12} aryl, 5- to 12-membered heteroaryl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{2-12} alkylaminoalkyl, C_{2-12} alkoxyalkyl, 3- to 12-membered heterocycloalkyl, 5- to 12-membered heteroaryl, and 3- to 12-membered heterocycloalkenyl;

[0069] wherein R^{11a} and R^{11b} are independently selected from the group consisting of hydrido, C_{5-12} aryl, 5- to 12-membered heteroaryl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{2-12} alkylaminoalkyl, C_{1-6} alkoxy, C_{2-12} alkoxyalkyl, 3- to 12-membered heterocycloalkyl, 5- to 12-membered heteroaryl, and 3- to 12-membered heterocycloalkenyl;

[0070] wherein R^2 and R^4 may form a 4- to 6-membered heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting of S, SO, SO_2, O, N, and NR^6;

[0071] wherein R^{7a} and R^{7b} may be taken together to form a 3- to 7-membered heterocyclic moiety having 1 to 3 heteroatoms selected from the group consisting of S, SO, SO_2, O, N, and NR^{8a}; and

[0072] wherein R^{9a} and R^{9b} may be taken together to form a 3- to 7-membered heterocyclic moiety having 1 to 3 heteroatoms selected from the group consisting of S, SO, SO_2, O, N, and NR^{8a};

[0073] or a pharmaceutically acceptable salt thereof.

[0074] In one particularly preferred embodiment, the compound of Formula I is a compound wherein X is selected from the group consisting of phenyl, biphenyl, naphthyl, and indenyl, wherein X is substituted by R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e};

[0075] wherein A is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, phenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, dihydropyridinyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, and pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, wherein A is optionally substituted by one or more substituents independently selected from the group consisting of R^3;

[0076] wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, and R^3 are independently selected from the group consisting of hydrido, cyano, hydroxyl, nitro, halo, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, chloromethoxy, dichloromethoxy, trichloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, phenyl, biphenyl, naphthyl, indenyl, ethenyl, propenyl, butenyl, pentenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, methylcarbonylamino, ethylcarbonylamino, propylcarbonylamino, butylcarbonylamino, pentylcarbonylamino, hexylcarbonylamino, phenylcarbonylamino, benzylcarbonylamino, $-OR^{10}$, $-SR^{7a}$, $-SO_2N(R^{7a})R^{7b}$, $-NR^{8a}R^{8b}$, $-NR^{8a}COR^{8c}$, $-NR^{8a}CO(OR^{8c})$, $-NR^{8a}SO_2R^{9a}$, $-NR^{8a}SO_2N(R^{9a})R^{9b}$, $-NR^{8a}CON(R^{9a})R^{9b}$, $-COR^{8a}$, $-CO_2R^{7a}$, and $-CON(R^{7a})R^{7b}$, wherein said phenyl, biphenyl, naphthyl, indenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, ethenyl, propenyl, butenyl, or pentenyl may be substituted with one or more substituents selected from the group consisting of R^{8a};

[0077] wherein R^4 is selected from the group consisting of cyano, $-CO_2R^{5a}$, and $-CH_2OR^{5a}$, $CONR^{5a}R^{5b}$;

[0078] wherein R^{5a}, R^{5b}, and R^6 are independently selected from the group consisting of hydrido, hydroxyl, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl;

[0079] wherein R^{7a} and R^{7b} are independently selected from the group consisting of hydrido, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, benzyl, phenylethyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, benzylamino, phenylethylamino, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, propylaminohexyl, N,N-dimethylaminomethyl, N,N-dimethylaminoethyl, N-methyl-N-ethylaminomethyl, N-methyl-N-ethylaminoethyl, N-methyl-N-propylaminomethyl, N-methyl-N-propylaminoethyl, N,N-diethylaminomethyl, N,N-diethylaminoethyl, N-ethyl-N-propylaminomethyl, N-ethyl-N-propylaminoethyl, N,N-dipropylaminomethyl, N,N-dipropylaminoethyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, pentenyl, ethynyl, propynyl, butynyl, pentynyl, pyridinylmethyl, pyridinylethyl,

benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, and isoindoledionylethyl;

[0080] wherein R^{8a} and R^{8b} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, pentyl, hexyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, benzyl, phenylethyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, benzylamino, phenylethylamino, amino, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, aminomethylcarbonyl, aminoethylcarbonyl, aminopropylcarbonyl, aminobutylcarbonyl, aminopentylcarbonyl, aminohexylcarbonyl, aminophenylcarbonyl, aminobenzylcarbonyl, pyridinylmethyl, pyridinylethyl, benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, and isoindoledionylethyl, wherein said methyl, ethyl, propyl, butyl, pentyl, hexyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, aminomethyl,

aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, benzyl, or phenylethyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate, isothiocyanate, methyl, ethyl, propyl, butyl, pentyl, hexyl, methylthio, ethylthio, propylthio, butylthio, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, N-methylamino, N-ethylamino, N-propylamino, methylsulfonamido, ethylsulfonamido, propylsulfonamido, butylsulfonamido, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, propylaminohexyl, methoxy, ethoxy, propoxy, butoxy, chloro, fluoro, bromo, iodo, methylcarbonyloxy, ethylcarbonyloxy, propylcarbonyloxy, butylcarbonyloxy, pentylcarbonyloxy, hexylcarbonyloxy, phenylcarbonyloxy, benzylcarbonyloxy, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethoxy, dichloromethoxy, trichloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcarbonyl, hexylcarbonyl, phenylcarbonyl, benzylcarbonyl, hydroxymethoxy, hydroxyethoxy, hydroxypropoxy, hydroxybutoxy, N,N-dimethylaminomethylcarbonyl, N,N-dimethylaminoethylcarbonyl, N,N-dimethylaminophenylcarbonyl, N-methyl-N-ethylaminomethylcarbonyl, N-methyl-N-ethylaminoethylcarbonyl, N-methyl-N-ethylaminophenylcarbonyl, N-methyl-N-propylaminomethylcarbonyl, N-methyl-N-propylaminoethylcarbonyl, N-methyl-N-propylaminophenylcarbonyl, N,N-diethylaminomethylcarbonyl, N,N-diethylaminoethylcarbonyl, N,N-diethylaminophenylcarbonyl, N-ethyl-N-propylaminomethylcarbonyl, N-ethyl-N-propylaminoethylcarbonyl, N-ethyl-N-

propylaminophenylcarbonyl, N,N-dipropylaminomethylcarbonyl, N,N-dipropylaminoethylcarbonyl, N,N-dipropylaminophenylcarbonyl, thiomethyl, thioethyl, thiopropyl, thiobutyl, thiopentyl, thiohexyl, aminomethylcarbonyloxy, aminoethylcarbonyloxy, aminopropylcarbonyloxy, aminobutylcarbonyloxy, aminopentylcarbonyloxy, aminohexylcarbonyloxy, aminophenylcarbonyloxy, aminobenzylcarbonyloxy, methyldioxy, ethyldioxy, propyldioxy, butyldioxy, pentyldioxy, hexyldioxy, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, N-methylamino, N-ethylamino, N-propylamino, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, butoxyethyl, butoxypropyl, ethenylamino, propenylamino, butenylamino, pentenylamino, ethynylamino, propynylamino, butynylamino, pentynylamino, ethenyl, propenyl, butenyl, pentenyl, ethynyl, propynyl, butynyl, pentynyl, N,N-dimethylaminomethoxy, N,N-dimethylaminoethoxy, N-methyl-N-ethylaminomethoxy, N-methyl-N-ethylaminoethoxy, N-methyl-N-propylaminomethoxy, N-methyl-N-propylaminoethoxy, N,N-diethylaminomethoxy, N,N-diethylaminoethoxy, N-ethyl-N-propylaminomethoxy, N-ethyl-N-propylaminoethoxy, N,N-dipropylaminomethoxy, N,N-dipropylaminoethoxy, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl, wherein said piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl,

isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, or isoindoledionyl may be substituted with a substituent selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, N-methylamino, N-ethylamino, N-propylamino, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, and propylaminohexyl;

[0081] wherein R^{8c} is selected from the group consisting of hydrido, nitro, azido, methyl, ethyl, propyl, butyl, pentyl, hexyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, benzyl, phenylethyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, benzylamino, phenylethylamino, amino, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, aminomethylcarbonyl, aminoethylcarbonyl, aminopropylcarbonyl, aminobutylcarbonyl, aminopentylcarbonyl, aminohexylcarbonyl, aminophenylcarbonyl, aminobenzylcarbonyl, pyridinylmethyl, pyridinylethyl, benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl,

isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, and isoindoledionylethyl, wherein said methyl, ethyl, propyl, butyl, pentyl, hexyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, benzyl, or phenylethyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate, isothiocyanate, methyl, ethyl, propyl, butyl, pentyl, hexyl, methylthio, ethylthio, propylthio, butylthio, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, N-methylamino, N-ethylamino, N-propylamino, methylsulfonamido, ethylsulfonamido, propylsulfonamido, butylsulfonamido, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, propylaminohexyl, methoxy, ethoxy, propoxy, butoxy, chloro, fluoro, bromo, iodo, methylcarbonyloxy, ethylcarbonyloxy, propylcarbonyloxy, butylcarbonyloxy, pentylcarbonyloxy, hexylcarbonyloxy, phenylcarbonyloxy, benzylcarbonyloxy, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethoxy, dichloromethoxy, trichloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcarbonyl, hexylcarbonyl, phenylcarbonyl, benzylcarbonyl, hydroxymethoxy, hydroxyethoxy, hydroxypropoxy, hydroxybutoxy, N,N-dimethylaminomethylcarbonyl, N,N-dimethylaminoethylcarbonyl, N,N-dimethylaminophenylcarbonyl, N-methyl-N-ethylaminomethylcarbonyl, N-

methyl-N-ethylaminoethylcarbonyl, N-methyl-N-ethylaminophenylcarbonyl, N-methyl-N-propylaminomethylcarbonyl, N-methyl-N-propylaminoethylcarbonyl, N-methyl-N-propylaminophenylcarbonyl, N,N-diethylaminomethylcarbonyl, N,N-diethylaminoethylcarbonyl, N,N-diethylaminophenylcarbonyl, N-ethyl-N-propylaminomethylcarbonyl, N-ethyl-N-propylaminoethylcarbonyl, N-ethyl-N-propylaminophenylcarbonyl, N,N-dipropylaminomethylcarbonyl, N,N-dipropylaminoethylcarbonyl, N,N-dipropylaminophenylcarbonyl, thiomethyl, thioethyl, thiopropyl, thiobutyl, thiopentyl, thiohexyl, aminomethylcarbonyloxy, aminoethylcarbonyloxy, aminopropylcarbonyloxy, aminobutylcarbonyloxy, aminopentylcarbonyloxy, aminohexylcarbonyloxy, aminophenylcarbonyloxy, aminobenzylcarbonyloxy, methyldioxy, ethyldioxy, propyldioxy, butyldioxy, pentyldioxy, hexyldioxy, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, N-methylamino, N-ethylamino, N-propylamino, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, butoxyethyl, butoxypropyl, ethenylamino, propenylamino, butenylamino, pentenylamino, ethynylamino, propynylamino, butynylamino, pentynylamino, ethenyl, propenyl, butenyl, pentenyl, ethynyl, propynyl, butynyl, pentynyl, N,N-dimethylaminomethoxy, N,N-dimethylaminoethoxy, N-methyl-N-ethylaminomethoxy, N-methyl-N-ethylaminoethoxy, N-methyl-N-propylaminomethoxy, N-methyl-N-propylaminoethoxy, N,N-diethylaminomethoxy, N,N-diethylaminoethoxy, N-ethyl-N-propylaminomethoxy, N-ethyl-N-propylaminoethoxy, N,N-dipropylaminomethoxy, N,N-dipropylaminoethoxy, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl,

furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl, wherein said piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, or isoindoledionyl may be substituted with a substituent selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, N-methylamino, N-ethylamino, N-propylamino, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, and propylaminohexyl;

[0082] wherein R^{9a} and R^{9b} are independently selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, pentyl, hexyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, benzylamino, phenylethylamino, pyridinylmethyl, pyridinylethyl, benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl,

isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, isoindoledionylethyl, phenyl, biphenyl, naphthyl, indenyl, benzyl, and phenylethyl, wherein said phenyl, biphenyl, naphthyl, indenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, benzyl, or phenylethyl may be substituted with one or more radicals selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, methoxy, ethoxy, propoxy, butoxy, chloro, fluoro, bromo, iodo, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyano, chloromethoxy, dichloromethoxy, trichloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcarbonyl, hexylcarbonyl, phenylcarbonyl, benzylcarbonyl, carboxyl, hydroxy, hydroxymethoxy, hydroxyethoxy, hydroxypropoxy, hydroxybutoxy, phenoxy, benzyloxy, N,N-dimethylaminomethoxy, N,N-dimethylaminoethoxy, N-methyl-N-ethylaminomethoxy, N-methyl-N-ethylaminoethoxy, N-methyl-N-propylaminomethoxy, N-methyl-N-propylaminoethoxy, N,N-diethylaminomethoxy, N,N-diethylaminoethoxy, N-ethyl-N-propylaminomethoxy, N-ethyl-N-propylaminoethoxy, N,N-dipropylaminomethoxy, N,N-dipropylaminoethoxy, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, and dihydrooxazolyl;

[0083] wherein R^{10} is selected from the group consisting of hydrido, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, ethenyl, propenyl, butenyl, pentenyl, ethynyl, propynyl, butynyl, pentynyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, propylaminohexyl, methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, butoxyethyl, butoxypropyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, and dihydrooxazolyl;

[0084] wherein R^{11a} and R^{11b} are independently selected from the group consisting of hydrido, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, ethenyl, propenyl, butenyl, pentenyl, ethynyl, propynyl, butynyl, pentynyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, aminomethyl, aminoethyl,

aminopropyl, aminobutyl, aminopentyl, aminohexyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, propylaminohexyl, methoxy, ethoxy, propoxy, butoxy, methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, butoxyethyl, butoxypropyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, and dihydrooxazolyl;

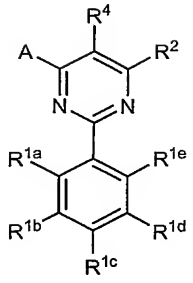
[0085] wherein R^2 and R^4 may form a 4- to 6-membered heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting of S, SO, SO_2, O, N, and NR^6;

[0086] wherein R^{7a} and R^{7b} may be taken together to form a 3- to 7-membered heterocyclic moiety having 1 to 3 heteroatoms selected from the group consisting of S, SO, SO_2, O, N, and NR^{8a}; and

[0087] wherein R^{9a} and R^{9b} may be taken together to form a 3- to 7-membered heterocyclic moiety having 1 to 3 heteroatoms selected from the group consisting of S, SO, SO_2, O, N, and NR^{8a};

[0088] or a pharmaceutically acceptable salt thereof.

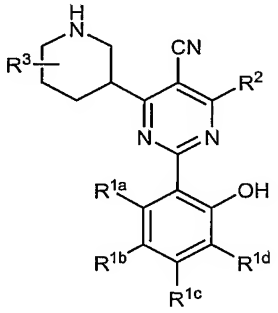
[0089] In a particularly preferred embodiment, the compound of Formula I is a compound of Formula II:



[0090] II

[0091] wherein A, R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^2, and R^4 are as defined above for Formula I; or a pharmaceutically acceptable salt thereof.

[0092] In a particularly preferred embodiment, the compound of Formula I is a compound of Formula III:



[0093] III

[0094] wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^3 are independently selected from the group consisting of hydrido, cyano, hydroxyl, nitro, halo, alkyl, haloalkyl, hydroxyalkyl, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, haloalkoxy, aryl, alkenyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, acylamino, $-OR^{10}$, $-SR^7$, $-SO_2NHR^7$, $-NHR^{8a}$, $-NR^{8a}COR^{8c}$, $-NR^{8a}CO(OR^{8c})$, $-NR^{8a}SO_2R^9$, $-NR^{8a}SO_2NHR^9$, $-NR^{8a}CONHR^9$, $-COR^{8a}$, $-CO_2R^7$, and $-CONHR^7$, wherein said aryl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, or alkenyl may be substituted with one or more substituents selected from the group consisting of R^{8a};

[0095] wherein R^2 is $-NHR^{11}$;

[0096] wherein R^7 is selected from the group consisting of hydrido, aryl, heteroaryl, aralkyl, heterocycloalkyl, heterocycloalkenyl, haloalkyl,

aralkylamino, alkylaminoalkyl, N,N-dialkylaminoacyl, alkyl, alkenyl, alkynyl, and heteroaralkyl;

[0097] wherein R^{8a} is selected from the group consisting of hydrido, alkyl, aryl, heteroaryl, aralkyl, heterocycloalkyl, heterocycloalkenyl, cycloalkyl, haloalkyl, aralkylamino, amino, aminoalkyl, aminoacyl, and heteroaralkyl, wherein said alkyl, aryl, heteroaryl, aminoalkyl, or aralkyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate, isothiocyanate, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylamino, alkylsulfonamido, aminoalkyl, alkylaminoalkyl, alkoxy, halo, acyloxy, haloalkyl, haloalkoxy, acyl, hydroxyalkoxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, alkyldioxy, hydroxyalkyl, N-alkylamino, alkoxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, N,N-dialkylaminoalkoxy, heterocycloalkyl, heterocycloalkenyl, and heteroaryl, wherein said heterocycloalkyl, heterocycloalkenyl, or heteroaryl substituents may be substituted with a substituent selected from the group consisting of alkyl, N-alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

[0098] wherein R^{8b} is selected from the group consisting of hydrido, nitro, azido, alkyl, aryl, heteroaryl, aralkyl, heterocycloalkyl, heterocycloalkenyl, cycloalkyl, haloalkyl, aralkylamino, amino, aminoalkyl, aminoacyl, and heteroaralkyl, wherein said alkyl, aryl, heteroaryl, aminoalkyl, or aralkyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate, isothiocyanate, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylamino, alkylsulfonamido, aminoalkyl, alkylaminoalkyl, alkoxy, halo, acyloxy, haloalkyl, haloalkoxy, acyl, hydroxyalkoxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, alkyldioxy, hydroxyalkyl, N-alkylamino, alkoxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, N,N-dialkylaminoalkoxy, heterocycloalkyl, heterocycloalkenyl, and

heteroaryl, wherein said heterocycloalkyl, heterocycloalkenyl, or heteroaryl substituents may be substituted with a substituent selected from the group consisting of alkyl, N-alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

[0099] wherein R^9 is selected from the group consisting of hydrido, alkyl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, haloalkyl, aralkylamino, heteroaralkyl, aryl, and aralkyl, wherein said aryl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, or aralkyl moieties may be substituted with one or more radicals selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkoxy, phenoxy, benzyloxy, N,N-dialkylaminoalkoxy, heteroaryl, heterocycloalkyl, and heterocycloalkenyl; and

[00100] wherein R^{10} is selected from the group consisting of hydrido, aryl, heteroaryl, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxyalkyl, heterocycloalkyl, heteroaryl, and heterocycloalkenyl;

[00101] wherein R^{11} is selected from the group consisting of hydrido, aryl, heteroaryl, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocycloalkyl, heteroaryl, and heterocycloalkenyl;

[00102] or a pharmaceutically acceptable salt thereof.

[00103] In one preferred embodiment, the compound of Formula III is a compound wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^3 are independently selected from the group consisting of hydrido, cyano, hydroxyl, nitro, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{2-7} alkoxycarbonyl, C_{1-6} haloalkoxy, C_{5-12} aryl, C_{2-6} alkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, 5- to 12-membered heteroaryl, C_{2-10} acylamino, $-OR^{10}$, $-SR^7$, $-SO_2NHR^7$, $-NHR^{8a}$, $-NR^{8a}COR^{8b}$, $-NR^{8a}CO(OR^{8b})$, $-NR^{8a}SO_2R^9$, $-NR^{8a}SO_2NHR^9$, $-NR^{8a}CONHR^9$, $-COR^{8a}$, $-CO_2R^7$, and $-CONHR^7$, wherein said aryl, heterocycloalkyl, heterocycloalkenyl,

heteroaryl, or alkenyl moiety may be substituted with one or more substituents selected from the group consisting of R^{8a};

[00104] wherein R^7 is selected from the group consisting of hydrido, C_{5-12} aryl, 5- to 12-membered heteroaryl, C_{4-18} aralkyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_{1-6} haloalkyl, C_{4-18} aralkylamino, C_{2-12} alkylaminoalkyl, N-N-di(C_{1-6} alkyl)amino(C_{1-6} alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and 4- to 18-membered heteroaralkyl;

[00105] wherein R^{8a} is selected from the group consisting of hydrido, C_{1-6} alkyl, C_{5-12} aryl, 5- to 12-membered heteroaryl, C_{4-18} aralkyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_{3-12} cycloalkyl, C_{1-6} haloalkyl, C_{4-18} aralkylamino, amino, C_{1-6} aminoalkyl, C_{2-10} aminoacyl, and 4- to 18-membered heteroaralkyl, wherein said alkyl, aryl, heteroaryl, aminoalkyl, or aralkyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate, isothiocyanate, C_{1-6} alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, N-(C_{1-6} alkyl)amino, C_{1-6} alkylsulfonamido, C_{1-6} aminoalkyl, C_{2-12} alkylaminoalkyl, C_{1-6} alkoxy, halo, C_{2-10} acyloxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-10} acyl, C_{1-6} hydroxyalkoxy, N,N-di(C_{1-6} alkyl)amino(C_{2-10} acyl), C_{1-6} thioalkyl, C_{2-10} aminoacyloxy, C_{1-6} alkyldioxy, C_{1-6} hydroxyalkyl, N-(C_{1-6} alkyl)amino, C_{2-7} alkoxycarbonyl, C_{2-12} alkoxyalkyl, C_{2-6} alkenylamino, C_{2-6} alkynylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, N,N-di(C_{1-6} alkyl)amino(C_{1-6} alkoxy), 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, and 5- to 12-membered heteroaryl, wherein said 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, or 5- to 12-membered heteroaryl moiety may be substituted with a substituent selected from the group consisting of C_{1-6} alkyl, N-(C_{1-6} alkyl)amino, C_{1-6} aminoalkyl, C_{1-6} hydroxyalkyl, and C_{2-12} alkylaminoalkyl;

[00106] wherein R^{8b} is selected from the group consisting of hydrido, nitro, azido, C_{1-6} alkyl, C_{5-12} aryl, 5- to 12-membered heteroaryl, C_{4-18} aralkyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_{3-12} cycloalkyl, C_{1-6} haloalkyl, C_{4-18} aralkylamino, amino, C_{1-6} aminoalkyl, C_{2-10} aminoacyl, and 4- to 18-membered heteroaralkyl, wherein said alkyl, aryl, heteroaryl, aminoalkyl, or aralkyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate, isothiocyanate, C_{1-6} alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, N-(C_{1-6} alkyl)amino, C_{1-6} alkylsulfonamido, C_{1-6} aminoalkyl, C_{2-12} alkylaminoalkyl, C_{1-6} alkoxy, halo, C_{2-10} acyloxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-10} acyl, C_{1-6} hydroxyalkoxy, N,N-di(C_{1-6} alkyl)amino(C_{2-10} acyl), C_{1-6} thioalkyl, C_{2-10} aminoacyloxy, C_{1-6} alkyldioxy, C_{1-6} hydroxyalkyl, N-(C_{1-6} alkyl)amino, C_{2-7} alkoxycarbonyl, C_{2-12} alkoxyalkyl, C_{2-6} alkenylamino, C_{2-6} alkynylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, N,N-di(C_{1-6} alkyl)amino(C_{1-6} alkoxy), 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, and 5- to 12-membered heteroaryl, wherein said 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, or 5- to 12-membered heteroaryl moiety may be substituted with a substituent selected from the group consisting of C_{1-6} alkyl, N-(C_{1-6} alkyl)amino, C_{1-6} aminoalkyl, C_{1-6} hydroxyalkyl, and C_{2-12} alkylaminoalkyl;

[00107] wherein R^{9} is selected from the group consisting of hydrido, C_{1-6} alkyl, 5- to 12-membered heteroaryl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_{1-6} haloalkyl, C_{4-18} aralkylamino, 4- to 18-membered heteroaralkyl, C_{5-12} aryl, and C_{4-18} aralkyl, wherein said aryl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, or aralkyl moiety may be substituted with one or more radicals selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, halo, C_{1-6} haloalkyl, cyano, C_{1-6} haloalkoxy, C_{2-10} acyl, carboxyl, hydroxy, C_{1-6} hydroxyalkoxy, phenoxy, benzyloxy, N,N-di(C_{1-6} alkyl)amino(C_{1-6}

alkoxy), 5- to 12-membered heteroaryl, 3- to 12-membered heterocycloalkyl, and 3- to 12-membered heterocycloalkenyl;

[00108] wherein R^{10} is selected from the group consisting of hydrido, C_{5-12} aryl, 5- to 12-membered heteroaryl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{2-12} alkylaminoalkyl, C_{2-12} alkoxyalkyl, 3- to 12-membered heterocycloalkyl, 5- to 12-membered heteroaryl, and 3- to 12-membered heterocycloalkenyl;

[00109] wherein R^{11} is selected from the group consisting of hydrido, C_{5-12} aryl, 5- to 12-membered heteroaryl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{2-12} alkylaminoalkyl, C_{1-6} alkoxy, C_{2-12} alkoxyalkyl, 3- to 12-membered heterocycloalkyl, 5- to 12-membered heteroaryl, and 3- to 12-membered heterocycloalkenyl;

[00110] or a pharmaceutically acceptable salt thereof.

[00111] In one particularly preferred embodiment, the compound of Formula III is a compound wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^3 are independently selected from the group consisting of hydrido, cyano, hydroxyl, nitro, halo, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, chloromethoxy, dichloromethoxy, trichloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, phenyl, biphenyl, naphthyl, indenyl, ethenyl, propenyl, butenyl, pentenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl,

methylcarbonylamino, ethylcarbonylamino, propylcarbonylamino, butylcarbonylamino, pentylcarbonylamino, hexylcarbonylamino, phenylcarbonylamino, benzylcarbonylamino, $-OR^{10}$, $-SR^{7}$, $-SO_2NHR^{7}$, $-NHR^{8a}$, $-NR^{8a}COR^{8b}$, $-NR^{8a}CO(OR^{8b})$, $-NR^{8a}SO_2R^{9}$, $-NR^{8a}SO_2NHR^{9}$, $-NR^{8a}CONHR^{9}$, $-COR^{8a}$, $-CO_2R^{7}$, and $-CONHR^{7}$, wherein said phenyl, biphenyl, naphthyl, indenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, ethenyl, propenyl, butenyl, or pentenyl may be substituted with one or more substituents selected from the group consisting of R^{8a};

[00112] wherein R^{7} is selected from the group consisting of hydrido, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, benzyl, phenylethyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, benzylamino, phenylethylamino, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, propylaminohexyl, N,N-dimethylaminomethyl, N,N-dimethylaminoethyl, N-methyl-N-ethylaminomethyl, N-methyl-N-ethylaminoethyl, N-methyl-N-propylaminomethyl, N-methyl-N-propylaminoethyl, N,N-diethylaminomethyl,

N,N-diethylaminoethyl, N-ethyl-N-propylaminomethyl, N-ethyl-N-propylaminoethyl, N,N-dipropylaminomethyl, N,N-dipropylaminoethyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, pentenyl, ethynyl, propynyl, butynyl, pentynyl, pyridinylmethyl, pyridinylethyl, benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, and isoindoledionylethyl;

[00113] wherein R^{8a} is selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, pentyl, hexyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, benzyl, phenylethyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, benzylamino, phenylethylamino, amino, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, aminomethylcarbonyl, aminoethylcarbonyl, aminopropylcarbonyl, aminobutylcarbonyl, aminopentylcarbonyl, aminohexylcarbonyl, aminophenylcarbonyl, aminobenzylcarbonyl, pyridinylmethyl, pyridinylethyl, benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl,

isoindoledionylmethyl, and isoindoledionylethyl, wherein said methyl, ethyl, propyl, butyl, pentyl, hexyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, benzyl, or phenylethyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate, isothiocyanate, methyl, ethyl, propyl, butyl, pentyl, hexyl, methylthio, ethylthio, propylthio, butylthio, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, N-methylamino, N-ethylamino, N-propylamino, methylsulfonamido, ethylsulfonamido, propylsulfonamido, butylsulfonamido, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, propylaminohexyl, methoxy, ethoxy, propoxy, butoxy, chloro, fluoro, bromo, iodo, methylcarbonyloxy, ethylcarbonyloxy, propylcarbonyloxy, butylcarbonyloxy, pentylcarbonyloxy, hexylcarbonyloxy, phenylcarbonyloxy, benzylcarbonyloxy, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethoxy, dichloromethoxy, trichloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcarbonyl, hexylcarbonyl, phenylcarbonyl, benzylcarbonyl, hydroxymethoxy, hydroxyethoxy, hydroxypropoxy, hydroxybutoxy, N,N-dimethylaminomethylcarbonyl, N,N-dimethylaminoethylcarbonyl, N,N-dimethylaminophenylcarbonyl, N-methyl-N-ethylaminomethylcarbonyl, N-methyl-N-ethylaminoethylcarbonyl, N-methyl-N-ethylaminophenylcarbonyl, N-

methyl-N-propylaminomethylcarbonyl, N-methyl-N-propylaminoethylcarbonyl, N-methyl-N-propylaminophenylcarbonyl, N,N-diethylaminomethylcarbonyl, N,N-diethylaminoethylcarbonyl, N,N-diethylaminophenylcarbonyl, N-ethyl-N-propylaminomethylcarbonyl, N-ethyl-N-propylaminoethylcarbonyl, N-ethyl-N-propylaminophenylcarbonyl, N,N-dipropylaminomethylcarbonyl, N,N-dipropylaminoethylcarbonyl, N,N-dipropylaminophenylcarbonyl, thiomethyl, thioethyl, thiopropyl, thiobutyl, thiopentyl, thiohexyl, aminomethylcarbonyloxy, aminoethylcarbonyloxy, aminopropylcarbonyloxy, aminobutylcarbonyloxy, aminopentylcarbonyloxy, aminohexylcarbonyloxy, aminophenylcarbonyloxy, aminobenzylcarbonyloxy, methyldioxy, ethyldioxy, propyldioxy, butyldioxy, pentyldioxy, hexyldioxy, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, N-methylamino, N-ethylamino, N-propylamino, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, butoxyethyl, butoxypropyl, ethenylamino, propenylamino, butenylamino, pentenylamino, ethynylamino, propynylamino, butynylamino, pentynylamino, ethenyl, propenyl, butenyl, pentenyl, ethynyl, propynyl, butynyl, pentynyl, N,N-dimethylaminomethoxy, N,N-dimethylaminoethoxy, N-methyl-N-ethylaminomethoxy, N-methyl-N-ethylaminoethoxy, N-methyl-N-propylaminomethoxy, N-methyl-N-propylaminoethoxy, N,N-diethylaminomethoxy, N,N-diethylaminoethoxy, N-ethyl-N-propylaminomethoxy, N-ethyl-N-propylaminoethoxy, N,N-dipropylaminomethoxy, N,N-dipropylaminoethoxy, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl, wherein

said piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, or isoindoledionyl may be substituted with a substituent selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, N-methylamino, N-ethylamino, N-propylamino, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, and propylaminohexyl;

[00114] wherein R^{8b} is selected from the group consisting of hydrido, nitro, azido, methyl, ethyl, propyl, butyl, pentyl, hexyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, benzyl, phenylethyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, benzylamino, phenylethylamino, amino, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, aminomethylcarbonyl, aminoethylcarbonyl, aminopropylcarbonyl, aminobutylcarbonyl, aminopentylcarbonyl, aminohexylcarbonyl, aminophenylcarbonyl, aminobenzylcarbonyl, pyridinylmethyl, pyridinylethyl,

benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, and isoindoledionylethyl, wherein said methyl, ethyl, propyl, butyl, pentyl, hexyl, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, benzyl, or phenylethyl may be substituted with one or more substituents selected from the group consisting of oxy, formyl, cyano, carboxyl, hydroxy, sulfamyl, phenoxy, nitro, azido, benzyloxy, thiocyanate, isothiocyanate, methyl, ethyl, propyl, butyl, pentyl, hexyl, methylthio, ethylthio, propylthio, butylthio, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, N-methylamino, N-ethylamino, N-propylamino, methylsulfonamido, ethylsulfonamido, propylsulfonamido, butylsulfonamido, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, propylaminohexyl, methoxy, ethoxy, propoxy, butoxy, chloro, fluoro, bromo, iodo, methylcarbonyloxy, ethylcarbonyloxy, propylcarbonyloxy, butylcarbonyloxy, pentylcarbonyloxy, hexylcarbonyloxy, phenylcarbonyloxy, benzylcarbonyloxy, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethoxy, dichloromethoxy, trichloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcarbonyl,

hexylcarbonyl, phenylcarbonyl, benzylcarbonyl, hydroxymethoxy, hydroxyethoxy, hydroxypropoxy, hydroxybutoxy, N,N-dimethylaminomethylcarbonyl, N,N-dimethylaminoethylcarbonyl, N,N-dimethylaminophenylcarbonyl, N-methyl-N-ethylaminomethylcarbonyl, N-methyl-N-ethylaminoethylcarbonyl, N-methyl-N-ethylaminophenylcarbonyl, N-methyl-N-propylaminomethylcarbonyl, N-methyl-N-propylaminoethylcarbonyl, N-methyl-N-propylaminophenylcarbonyl, N,N-diethylaminomethylcarbonyl, N,N-diethylaminoethylcarbonyl, N,N-diethylaminophenylcarbonyl, N-ethyl-N-propylaminomethylcarbonyl, N-ethyl-N-propylaminoethylcarbonyl, N-ethyl-N-propylaminophenylcarbonyl, N,N-dipropylaminomethylcarbonyl, N,N-dipropylaminoethylcarbonyl, N,N-dipropylaminophenylcarbonyl, thiomethyl, thioethyl, thiopropyl, thiobutyl, thiopentyl, thiohexyl, aminomethylcarbonyloxy, aminoethylcarbonyloxy, aminopropylcarbonyloxy, aminobutylcarbonyloxy, aminopentylcarbonyloxy, aminohexylcarbonyloxy, aminophenylcarbonyloxy, aminobenzylcarbonyloxy, methyldioxy, ethyldioxy, propyldioxy, butyldioxy, pentyldioxy, hexyldioxy, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, N-methylamino, N-ethylamino, N-propylamino, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, butoxyethyl, butoxypropyl, ethenylamino, propenylamino, butenylamino, pentenylamino, ethynylamino, propynylamino, butynylamino, pentynylamino, ethenyl, propenyl, butenyl, pentenyl, ethynyl, propynyl, butynyl, pentynyl, N,N-dimethylaminomethoxy, N,N-dimethylaminoethoxy, N-methyl-N-ethylaminomethoxy, N-methyl-N-ethylaminoethoxy, N-methyl-N-propylaminomethoxy, N-methyl-N-propylaminoethoxy, N,N-diethylaminomethoxy, N,N-diethylaminoethoxy, N-ethyl-N-propylaminomethoxy, N-ethyl-N-propylaminoethoxy, N,N-dipropylaminomethoxy, N,N-dipropylaminoethoxy, piperidinyl, pyrrolidinyl,

pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, and isoindoledionyl, wherein said piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, or isoindoledionyl may be substituted with a substituent selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, N-methylamino, N-ethylamino, N-propylamino, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, and propylaminohexyl;

[00115] wherein R^9 is selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, pentyl, hexyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, benzylamino, phenylethylamino, pyridinylmethyl, pyridinylethyl,

benzothiophenylmethyl, benzothiophenylethyl, indolylmethyl, indolylethyl, isoquinolinylmethyl, isoquinolinylethyl, quinolinylmethyl, quinolinylethyl, thienylmethyl, thienylethyl, pyrrolylmethyl, pyrrolylethyl, furylmethyl, furylethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, isoxazolylmethyl, isoxazolylethyl, oxazolylmethyl, oxazolylethyl, isoindoledionylmethyl, isoindoledionylethyl, phenyl, biphenyl, naphthyl, indenyl, benzyl, and phenylethyl, wherein said phenyl, biphenyl, naphthyl, indenyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, dihydrooxazolyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, benzyl, or phenylethyl may be substituted with one or more radicals selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, methoxy, ethoxy, propoxy, butoxy, chloro, fluoro, bromo, iodo, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyano, chloromethoxy, dichloromethoxy, trichloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylcarbonyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcarbonyl, hexylcarbonyl, phenylcarbonyl, benzylcarbonyl, carboxyl, hydroxy, hydroxymethoxy, hydroxyethoxy, hydroxypropoxy, hydroxybutoxy, phenoxy, benzyloxy, N,N-dimethylaminomethoxy, N,N-dimethylaminoethoxy, N-methyl-N-ethylaminomethoxy, N-methyl-N-ethylaminoethoxy, N-methyl-N-propylaminomethoxy, N-methyl-N-propylaminoethoxy, N,N-diethylaminomethoxy, N,N-diethylaminoethoxy, N-ethyl-N-propylaminomethoxy, N-ethyl-N-propylaminoethoxy, N,N-dipropylaminomethoxy, N,N-dipropylaminoethoxy, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, piperidinyl, pyrrolidinyl, pyrazolidinyl,

imidazolidinyl, isoxazolidinyl, oxazolidinyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, and dihydrooxazolyl;

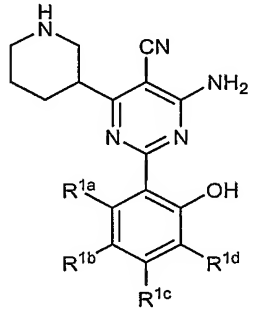
[00116] wherein R^{10} is selected from the group consisting of hydrido, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, ethenyl, propenyl, butenyl, pentenyl, ethynyl, propynyl, butynyl, pentynyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, propylaminohexyl, methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, butoxyethyl, butoxypropyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, and dihydrooxazolyl;

[00117] wherein R^{11} is selected from the group consisting of hydrido, phenyl, biphenyl, naphthyl, indenyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl,

trifluoromethyl, ethenyl, propenyl, butenyl, pentenyl, ethynyl, propynyl, butynyl, pentynyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, aminohexyl, methylaminomethyl, ethylaminomethyl, propylaminomethyl, methylaminoethyl, ethylaminoethyl, propylaminoethyl, methylaminopropyl, ethylaminopropyl, propylaminopropyl, methylaminobutyl, ethylaminobutyl, propylaminobutyl, methylaminopentyl, ethylaminopentyl, propylaminopentyl, methylaminohexyl, ethylaminohexyl, propylaminohexyl, methoxy, ethoxy, propoxy, butoxy, methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, butoxyethyl, butoxypropyl, piperidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, pyridinyl, benzothiophenyl, indolyl, isoquinolinyl, quinolinyl, thienyl, pyrrolyl, furyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isoindoledionyl, isoindolyl, dihydroindolyl, isoindoline, dihydrothiophenyl, dihydropyrrolyl, dihydrofuryl, dihydropyrazolyl, dihydroimidazolyl, dihydroisoxazolyl, and dihydrooxazolyl;

[00118] or a pharmaceutically acceptable salt thereof.

[00119] In another particularly preferred embodiment, the compound of Formula I is a compound of Formula IV:



[00120] IV

[00121] wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are independently selected from the group consisting of hydrido, cyano, hydroxyl, nitro, halo, alkyl, haloalkyl, hydroxyalkyl, haloalkoxy, $-OR^{10}$, $-NHR^{8}$, $-NHCOR^{8}$, $-NHCO(OR^{8})$, $-NHCONHR^{9}$, $-COR^{8}$, $-CO_2R^{7}$, and $-CONHR^{7}$; and

[00122] wherein R^7, R^8, R^9, and R^{10} are independently selected from the group consisting of hydrido, haloalkyl, alkyl, cycloalkyl, cycloalkylalkyl, and alkenyl;

[00123] or a pharmaceutically acceptable salt thereof.

[00124] In one preferred embodiment, the compound of Formula IV is a compound wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are independently selected from the group consisting of hydrido, cyano, hydroxyl, nitro, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkoxy, $-OR^{10}$, $-NHR^8$, $-NHCOR^8$, $-NHCO(OR^8)$, $-NHCONHR^9$, $-COR^8$, $-CO_2R^7$, and $-CONHR^7$; and

[00125] wherein R^7, R^8, R^9, and R^{10} are independently selected from the group consisting of hydrido, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{4-18} cycloalkylalkyl, and C_{2-6} alkenyl;

[00126] or a pharmaceutically acceptable salt thereof.

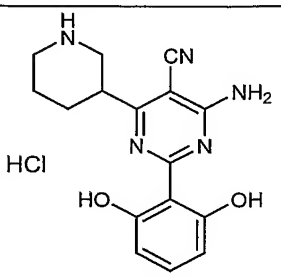
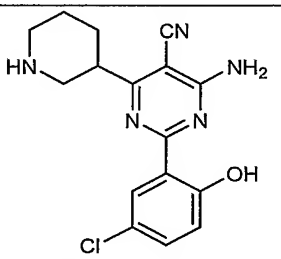
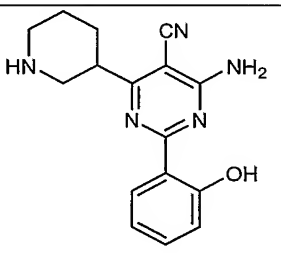
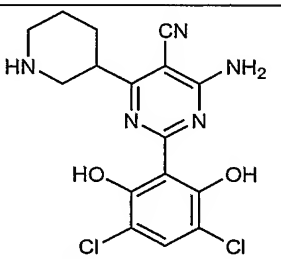
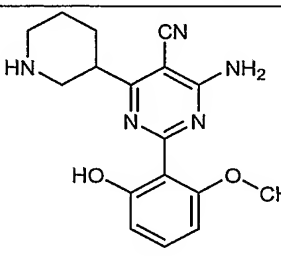
[00127] In one particularly preferred embodiment, the compound of Formula IV is a compound wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are independently selected from the group consisting of hydrido, cyano, hydroxyl, nitro, halo, methyl, ethyl, propyl, butyl, pentyl, hexyl, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, chloromethoxy, dichloromethoxy, trichloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, $-OR^{10}$, $-NHR^8$, $-NHCOR^8$, $-NHCO(OR^8)$, $-NHCONHR^9$, $-COR^8$, $-CO_2R^7$, and $-CONHR^7$; and

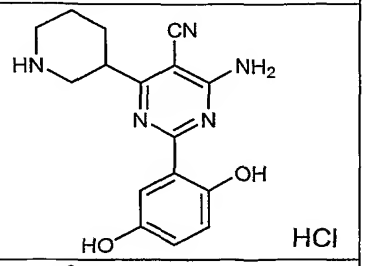
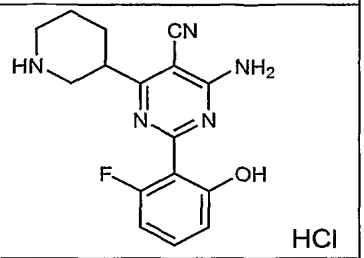
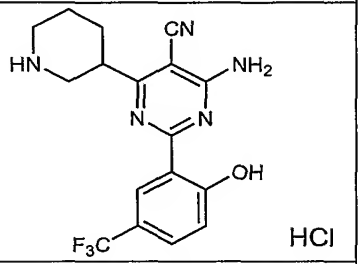
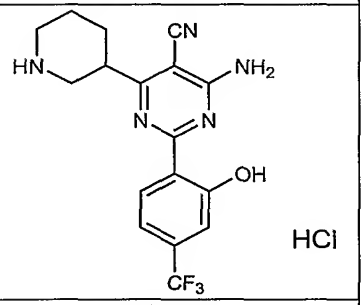
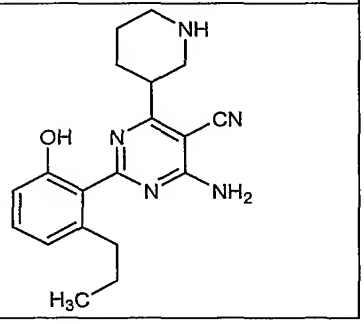
[00128] wherein R^7, R^8, R^9, and R^{10} are independently selected from the group consisting of hydrido, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, and ethenyl, propenyl, butenyl, and pentenyl;

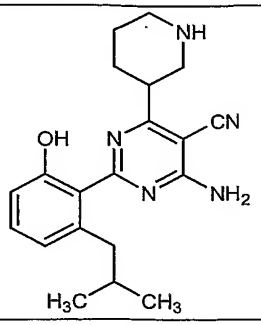
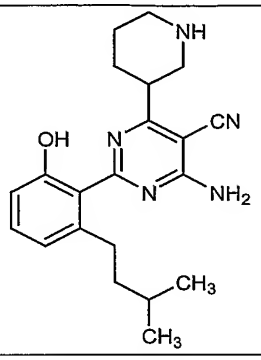
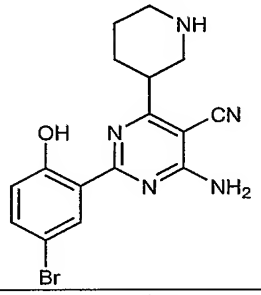
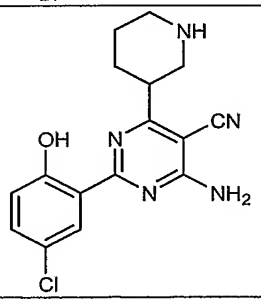
[00129] or a pharmaceutically acceptable salt thereof.

[00130] In a particularly preferred embodiment, the compound of Formula I is selected from the group of compounds consisting of the compounds shown in Table I below:

Table I

Example	Name	Structure
1	4-amino-2-(2,6-dihydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride	
3	4-amino-2-(5-chloro-2-hydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride	
4	4-amino-2-(2-hydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride	
5	4-amino-2-(3,5-dichloro-2,6-dihydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride	
6	4-amino-2-(2-hydroxy-6-methoxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride	

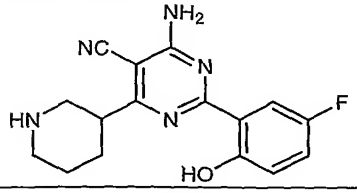
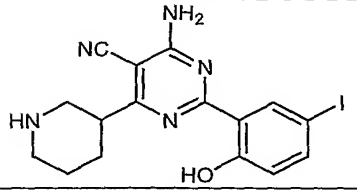
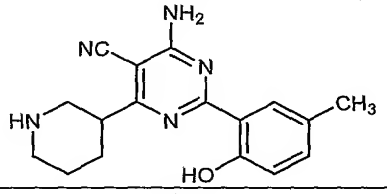
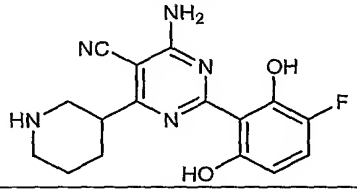
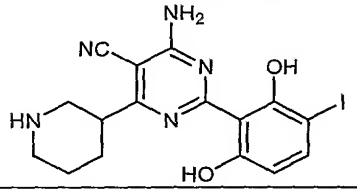
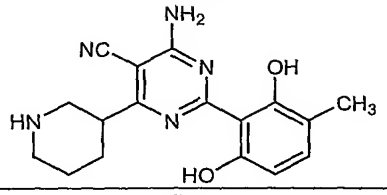
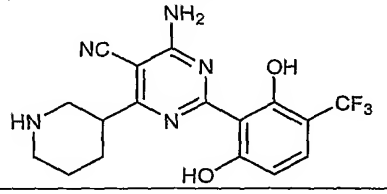
Example	Name	Structure
9	4-amino-2-(2,5-dihydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride	 HCl
10	4-amino-2-(2-fluoro-6-hydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride	 HCl
11	4-amino-2-[2-hydroxy-5-(trifluoromethyl)phenyl]-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride	 HCl
12	4-amino-2-[2-hydroxy-4-(trifluoromethyl)phenyl]-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride	 HCl
23	4-amino-2-(2-hydroxy-6-propylphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile	

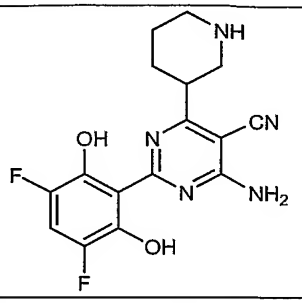
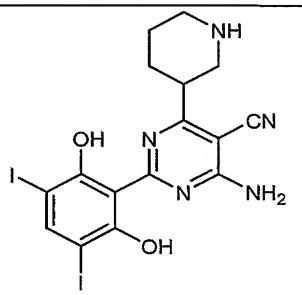
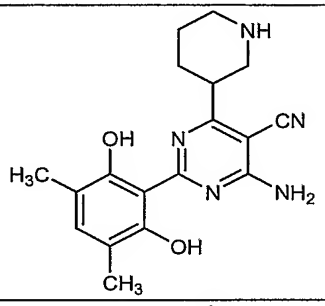
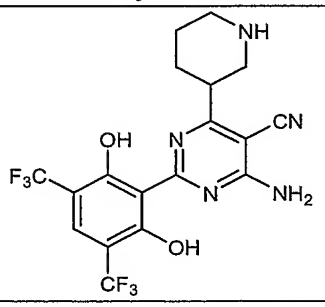
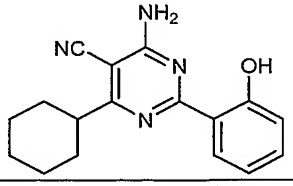
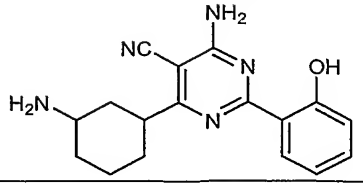
Example	Name	Structure
24	4-amino-2-(2-hydroxy-6-isobutylphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile	
25	4-amino-2-[2-hydroxy-6-(3-methylbutyl)phenyl]-6-piperidin-3-ylpyrimidine-5-carbonitrile	
29	4-amino-2-(5-bromo-2-hydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile	
30	4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile	

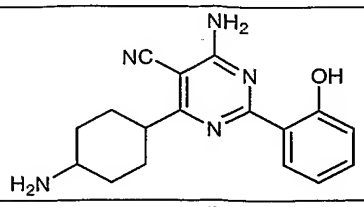
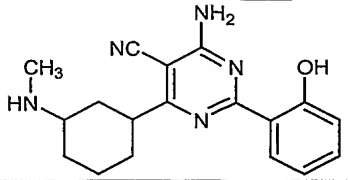
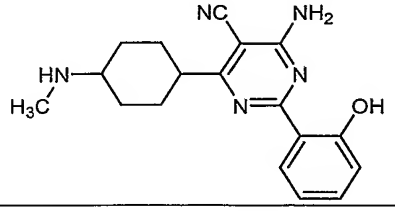
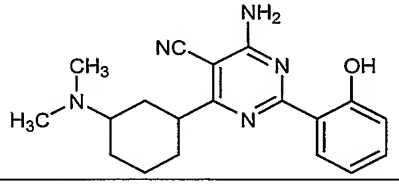
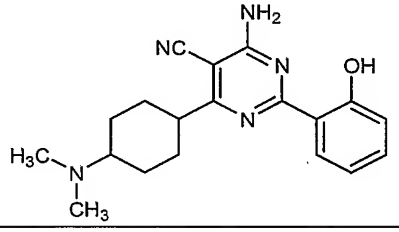
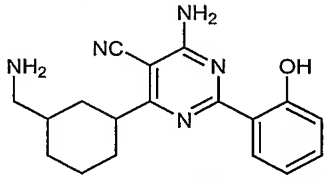
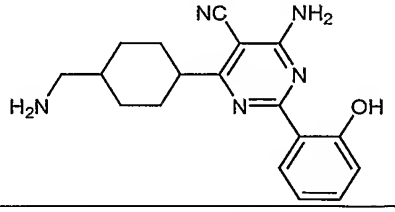
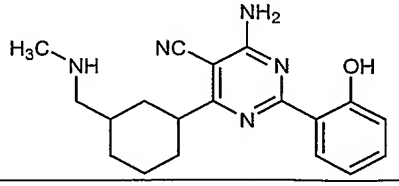
[00131] In another preferred embodiment, the compound of Formula I is selected from the group of compounds consisting of the compounds shown in Table II below:

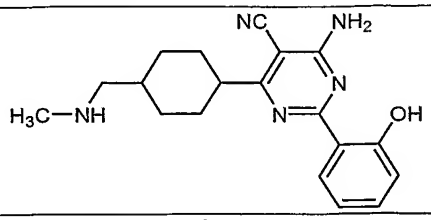
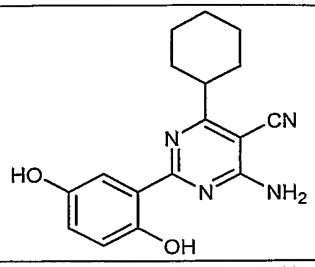
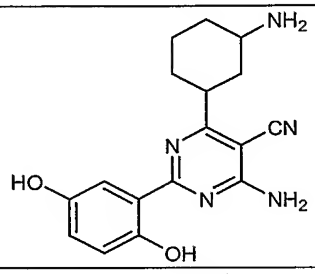
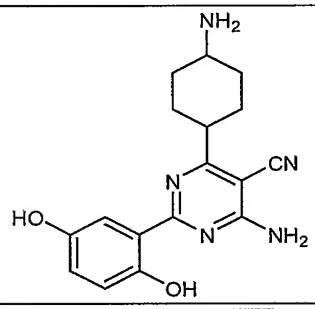
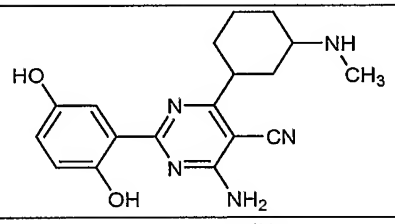
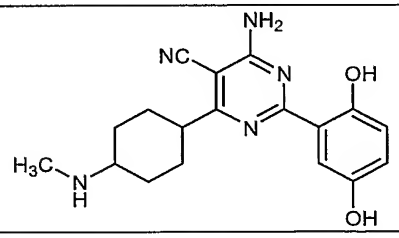
Table II

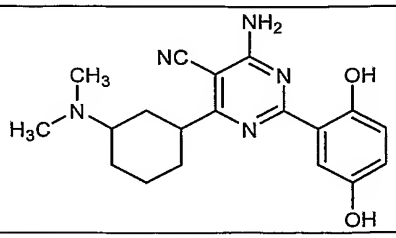
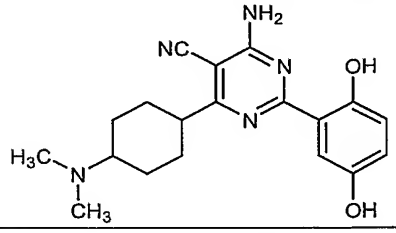
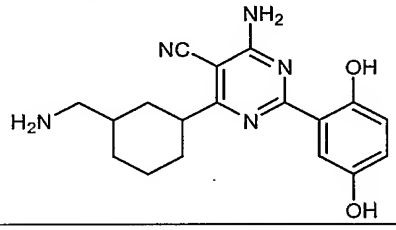
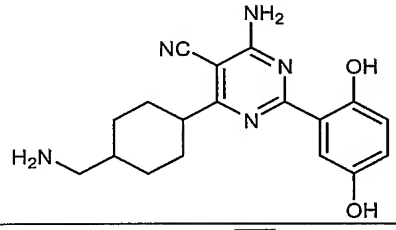
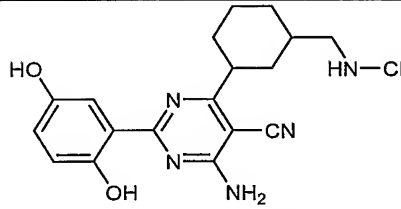
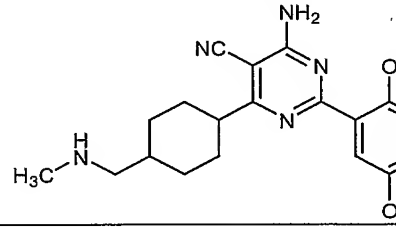
Name	Structure

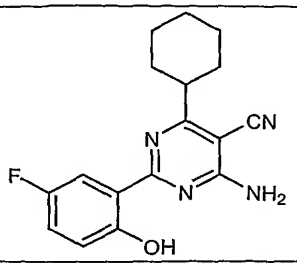
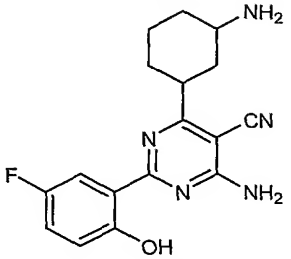
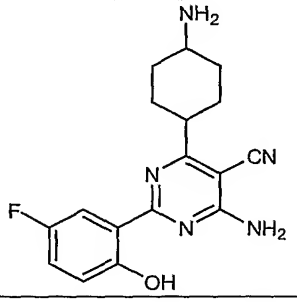
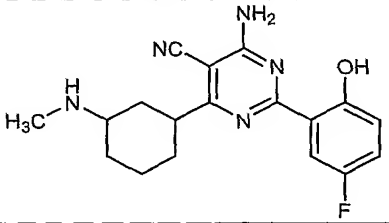
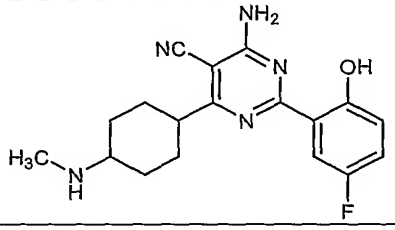
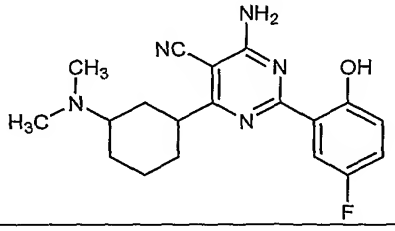
Name	Structure
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxy-5-iodophenyl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxy-5-methylphenyl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile	
4-amino-2-(3-fluoro-2,6-dihydroxyphenyl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile	
4-amino-2-(2,6-dihydroxy-3-iodophenyl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile	
4-amino-2-(2,6-dihydroxy-3-methylphenyl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile	
4-amino-2-(3-(trifluoromethyl)-2,6-dihydroxyphenyl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile	

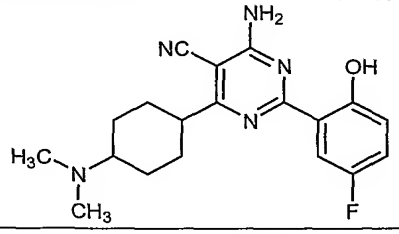
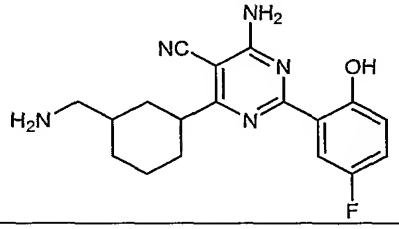
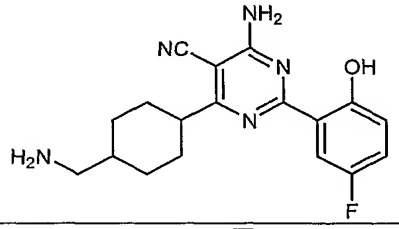
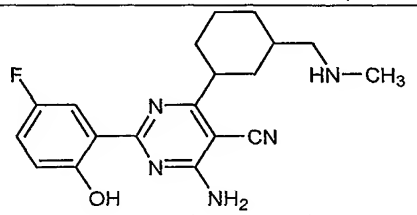
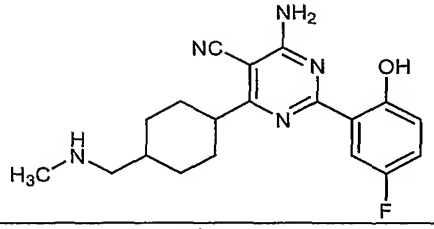
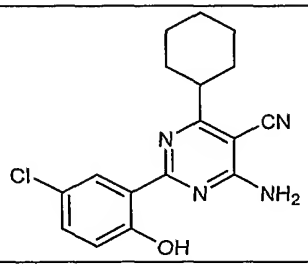
Name	Structure
4-amino-2-(3,5-difluoro-2,6-dihydroxyphenyl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile	
4-amino-2-(2,6-dihydroxy-3,5-diiodophenyl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile	
4-amino-2-(2,6-dihydroxy-3,5-dimethylphenyl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile	
2-(3,5-bis(trifluoromethyl)-2,6-dihydroxyphenyl)-4-amino-6-(piperidin-3-yl)pyrimidine-5-carbonitrile	
4-amino-6-cyclohexyl-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminocyclohexyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	

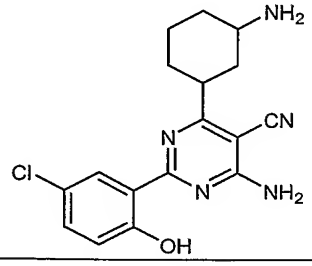
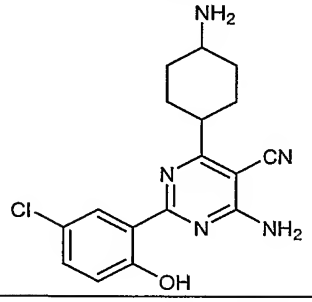
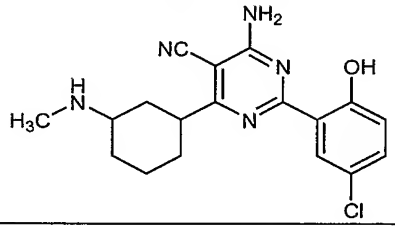
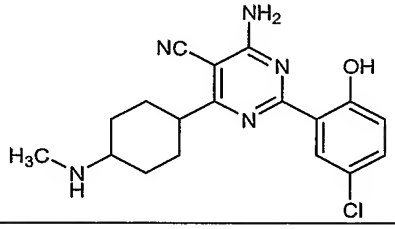
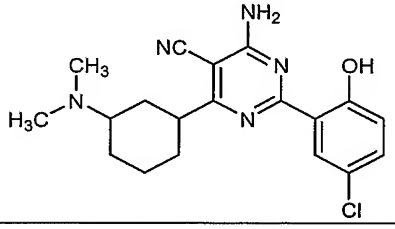
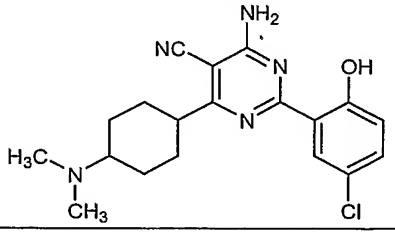
Name	Structure
4-amino-6-(4-aminocyclohexyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxyphenyl)-6-(3-(methylamino)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxyphenyl)-6-(4-(methylamino)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cyclohexyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(dimethylamino)cyclohexyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cyclohexyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)cyclohexyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxyphenyl)-6-(3-((methylamino)methyl)cyclohexyl)pyrimidine-5-carbonitrile	

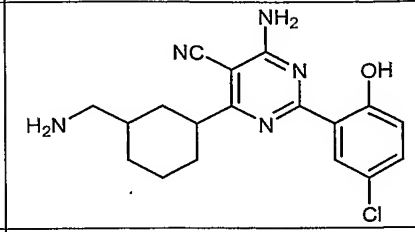
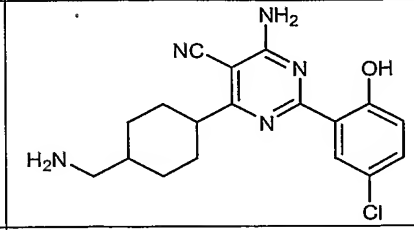
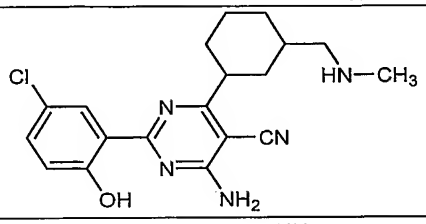
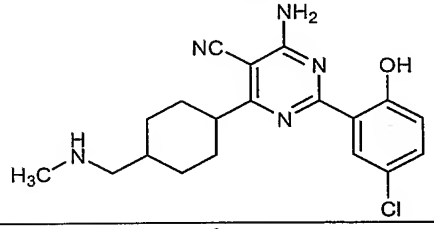
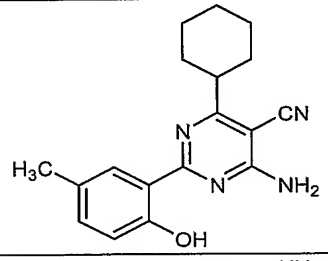
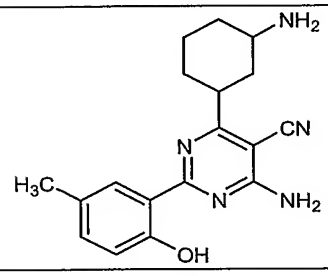
Name	Structure
4-amino-2-(2-hydroxyphenyl)-6-(4-((methylamino)methyl)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-6-cyclohexyl-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminocyclohexyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-aminocyclohexyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2,5-dihydroxyphenyl)-6-(3-(methylamino)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-2-(2,5-dihydroxyphenyl)-6-(4-(methylamino)cyclohexyl)pyrimidine-5-carbonitrile	

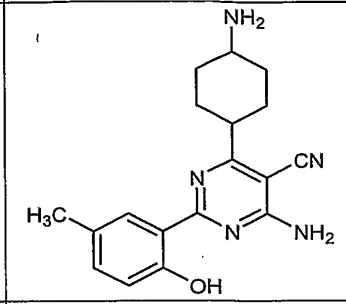
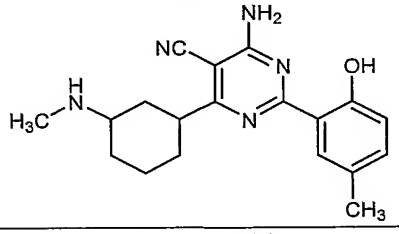
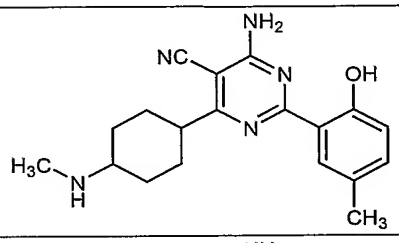
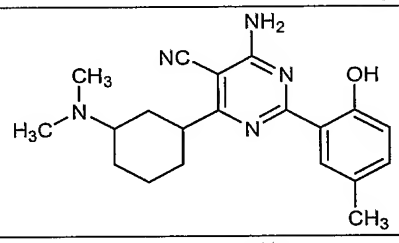
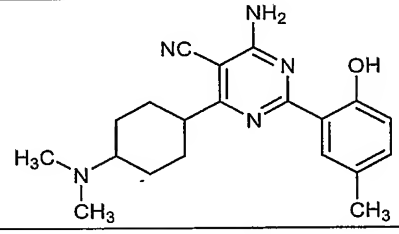
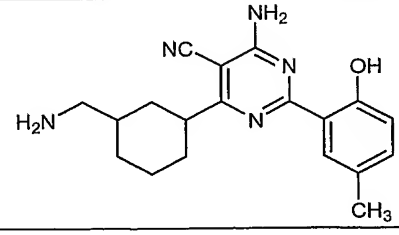
Name	Structure
4-amino-6-(3-(dimethylamino)cyclohexyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(dimethylamino)cyclohexyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cyclohexyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)cyclohexyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2,5-dihydroxyphenyl)-6-(3-((methylamino)methyl)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-2-(2,5-dihydroxyphenyl)-6-(4-((methylamino)methyl)cyclohexyl)pyrimidine-5-carbonitrile	

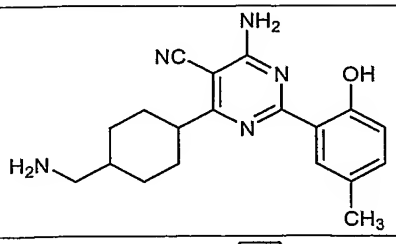
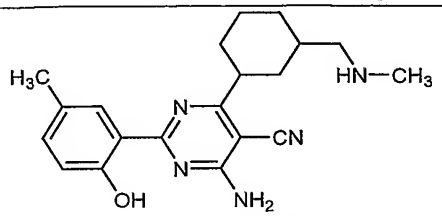
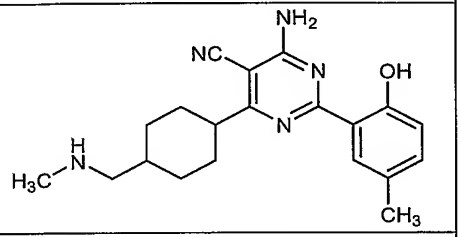
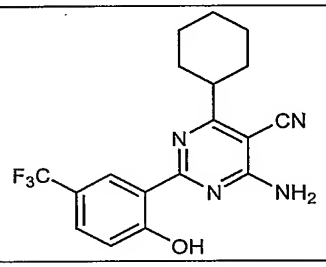
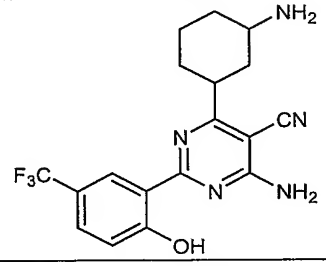
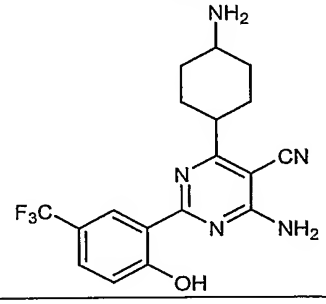
Name	Structure
4-amino-6-cyclohexyl-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminocyclohexyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-aminocyclohexyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(3-(methylamino)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(4-(methylamino)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cyclohexyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	

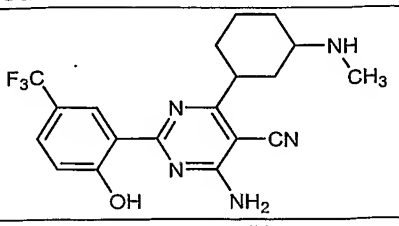
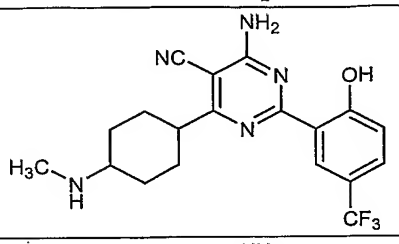
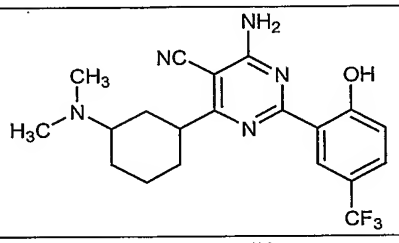
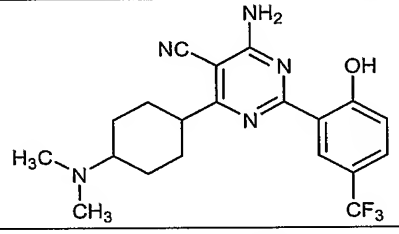
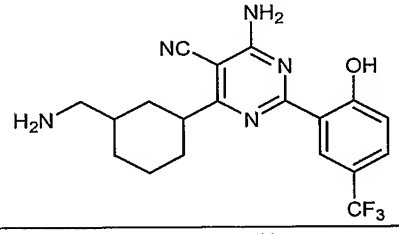
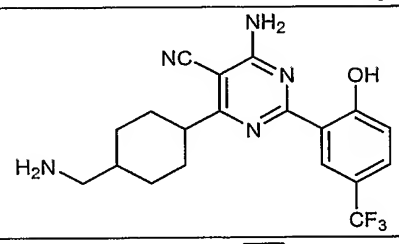
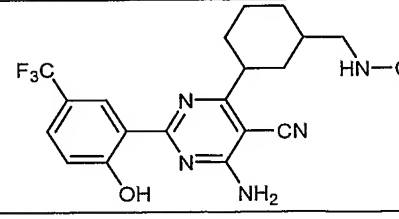
Name	Structure
4-amino-6-(4-(dimethylamino)cyclohexyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cyclohexyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)cyclohexyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(3-((methylamino)methyl)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(4-((methylamino)methyl)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-cyclohexylpyrimidine-5-carbonitrile	

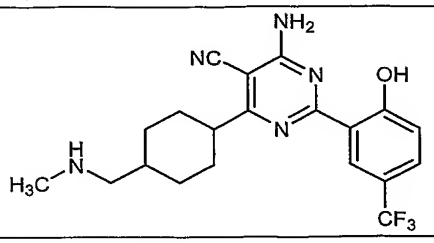
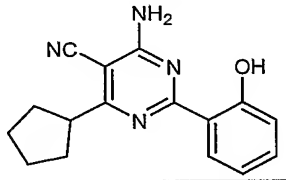
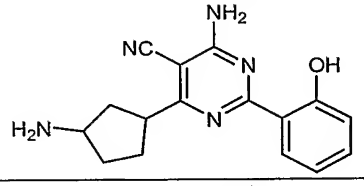
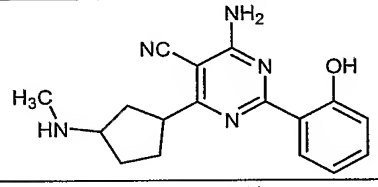
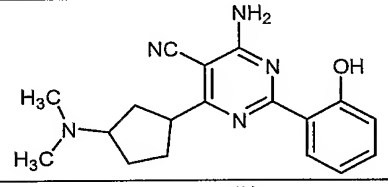
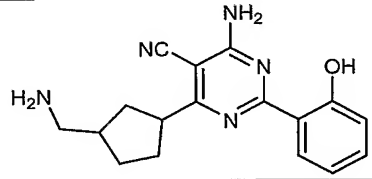
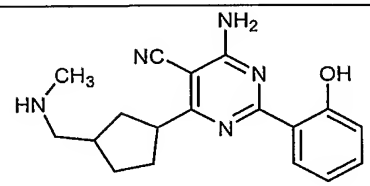
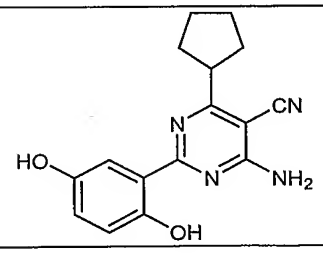
Name	Structure
4-amino-6-(3-aminocyclohexyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-aminocyclohexyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(3-(methylamino)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(4-(methylamino)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(3-(dimethylamino)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(4-(dimethylamino)cyclohexyl)pyrimidine-5-carbonitrile	

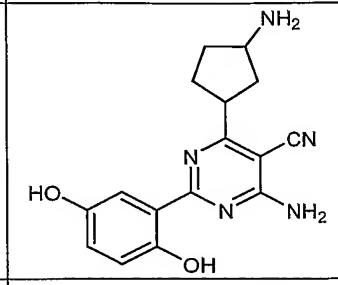
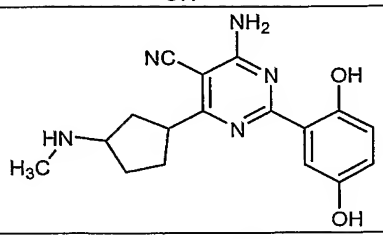
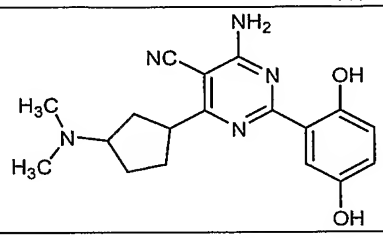
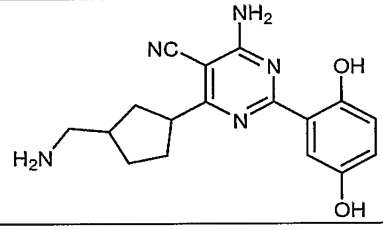
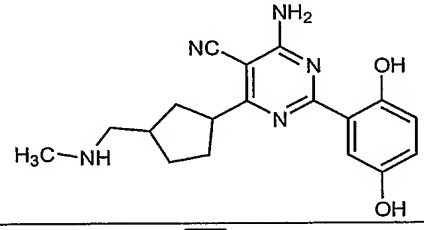
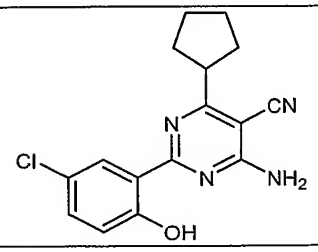
Name	Structure
4-amino-6-(3-(aminomethyl)cyclohexyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)cyclohexyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(3-((methylamino)methyl)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(4-((methylamino)methyl)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-6-cyclohexyl-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminocyclohexyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	

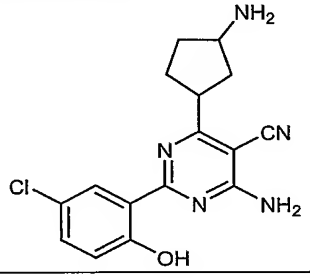
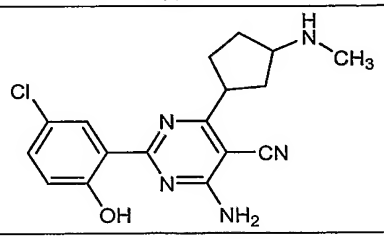
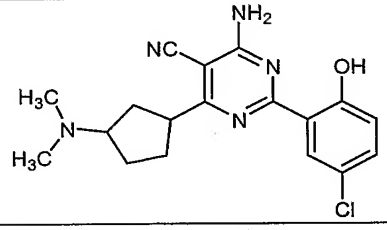
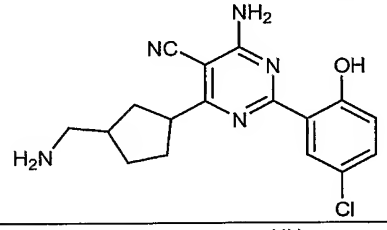
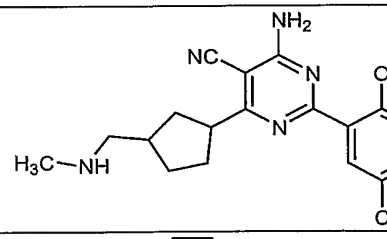
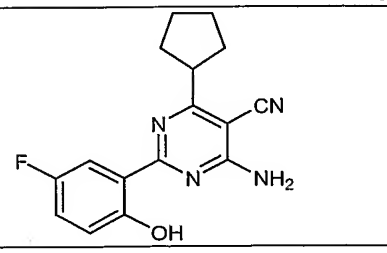
Name	Structure
4-amino-6-(4-aminocyclohexyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxy-5-methylphenyl)-6-(3-(methylamino)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxy-5-methylphenyl)-6-(4-(methylamino)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cyclohexyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(dimethylamino)cyclohexyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cyclohexyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	

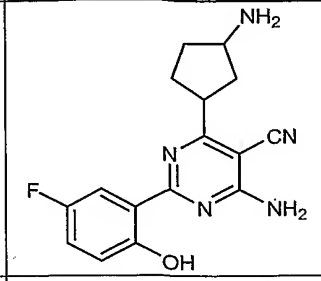
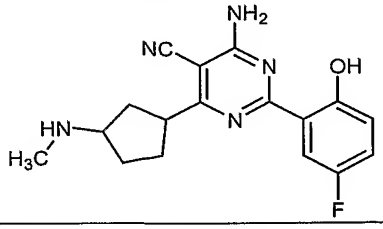
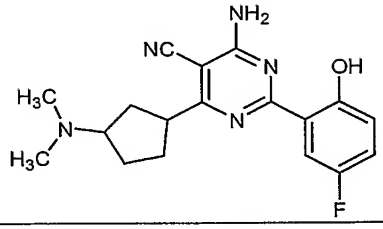
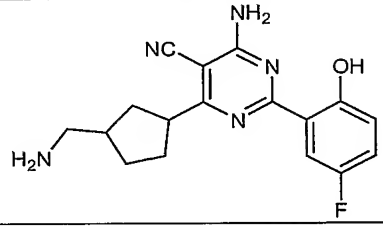
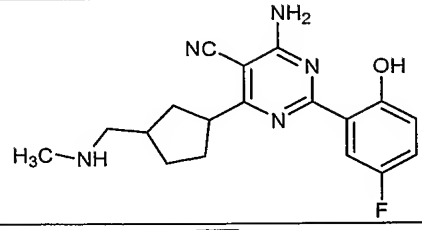
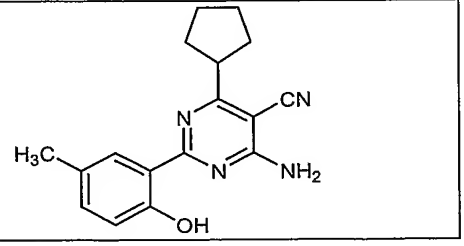
Name	Structure
4-amino-6-(4-(aminomethyl)cyclohexyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxy-5-methylphenyl)-6-(3-((methylamino)methyl)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxy-5-methylphenyl)-6-(4-((methylamino)methyl)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-6-cyclohexyl-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminocyclohexyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-aminocyclohexyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	

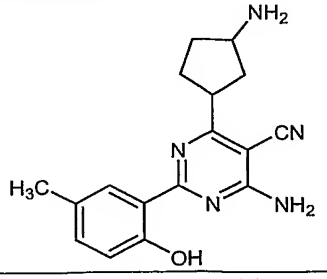
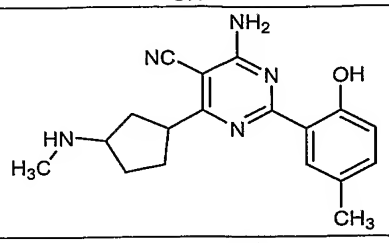
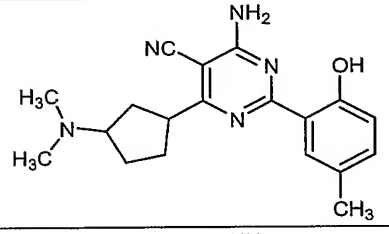
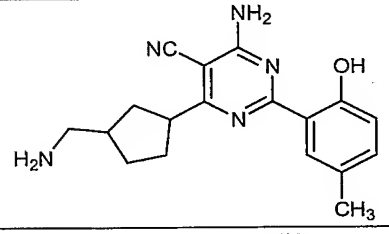
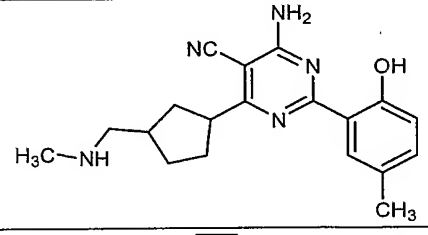
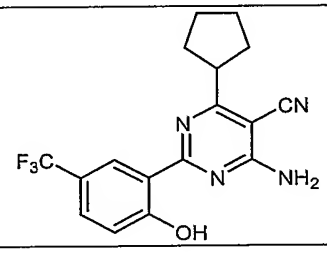
Name	Structure
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(3-(methylamino)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(4-(methylamino)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cyclohexyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(dimethylamino)cyclohexyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cyclohexyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)cyclohexyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(3-((methylamino)methyl)cyclohexyl)pyrimidine-5-carbonitrile	

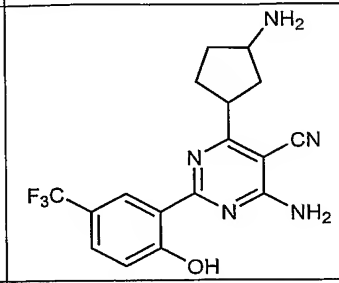
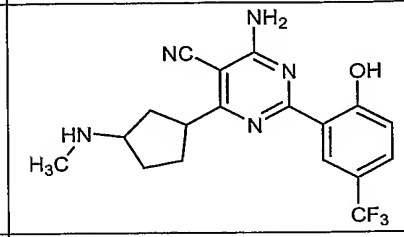
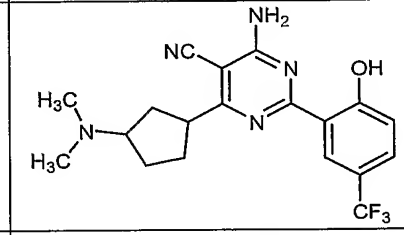
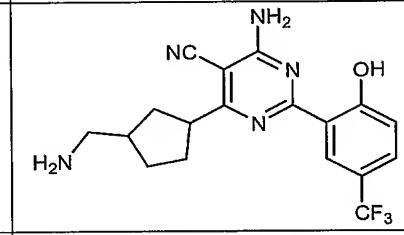
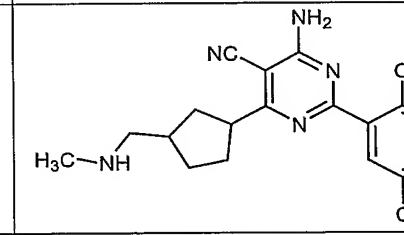
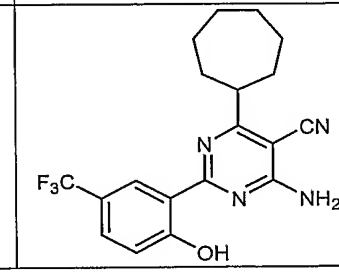
Name	Structure
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(4-((methylamino)methyl)cyclohexyl)pyrimidine-5-carbonitrile	
4-amino-6-cyclopentyl-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminocyclopentyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxyphenyl)-6-(3-(methylamino)cyclopentyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cyclopentyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cyclopentyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxyphenyl)-6-(3-((methylamino)methyl)cyclopentyl)pyrimidine-5-carbonitrile	
4-amino-6-cyclopentyl-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	

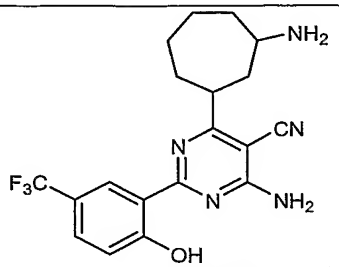
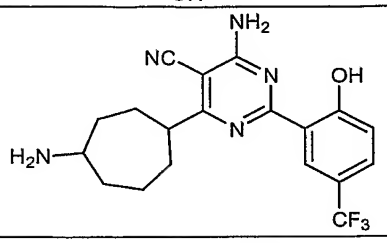
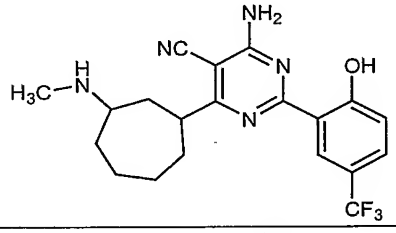
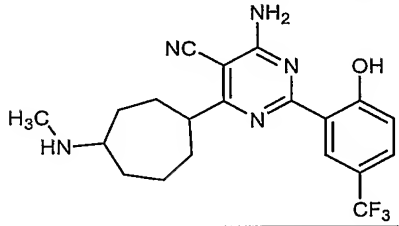
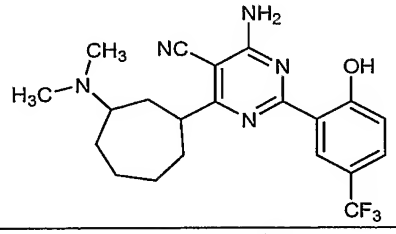
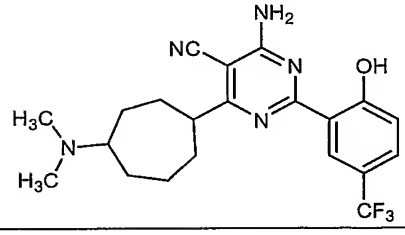
Name	Structure
4-amino-6-(3-aminocyclopentyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2,5-dihydroxyphenyl)-6-(3-(methylamino)cyclopentyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cyclopentyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cyclopentyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2,5-dihydroxyphenyl)-6-(3-((methylamino)methyl)cyclopentyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-cyclopentylpyrimidine-5-carbonitrile	

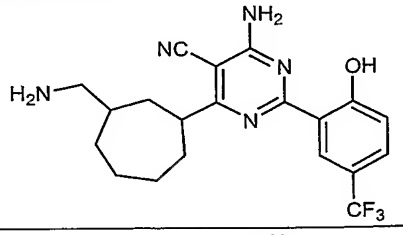
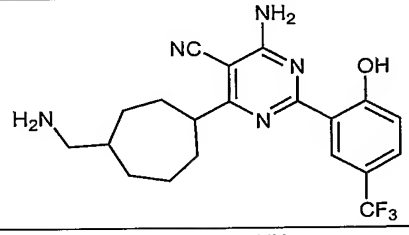
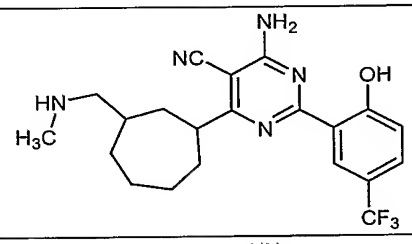
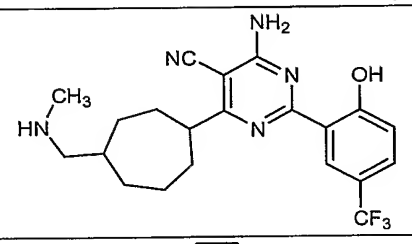
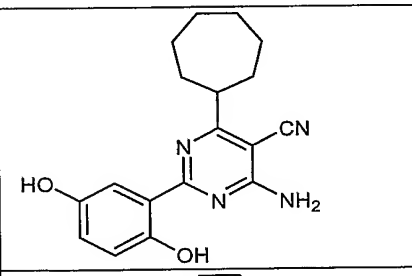
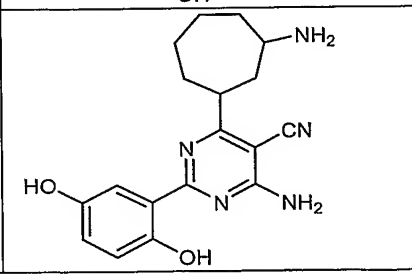
Name	Structure
4-amino-6-(3-aminocyclopentyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(3-(methylamino)cyclopentyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(3-(dimethylamino)cyclopentyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cyclopentyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(3-((methylamino)methyl)cyclopentyl)pyrimidine-5-carbonitrile	
4-amino-6-cyclopentyl-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	

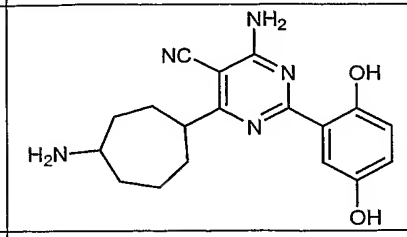
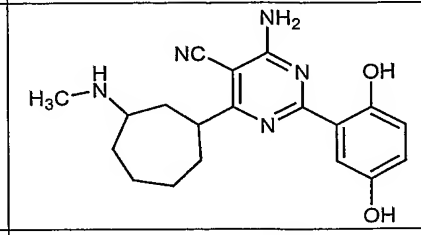
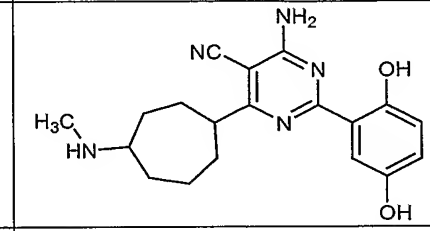
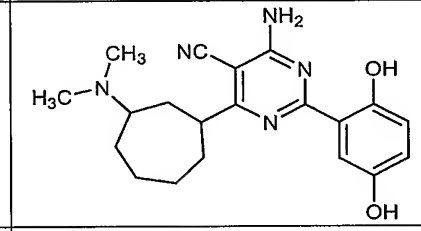
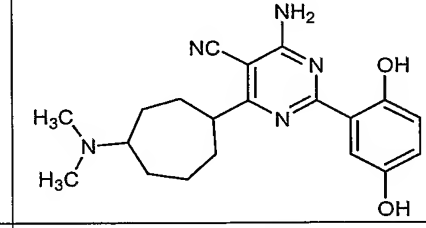
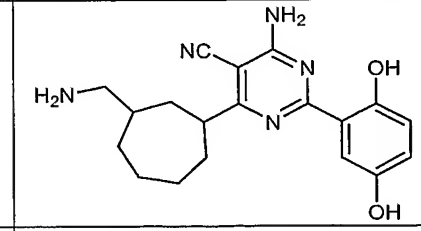
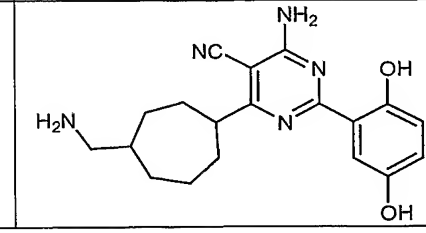
Name	Structure
4-amino-6-(3-aminocyclopentyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(3-(methylamino)cyclopentyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cyclopentyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cyclopentyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(3-((methylamino)methyl)cyclopentyl)pyrimidine-5-carbonitrile	
4-amino-6-cyclopentyl-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	

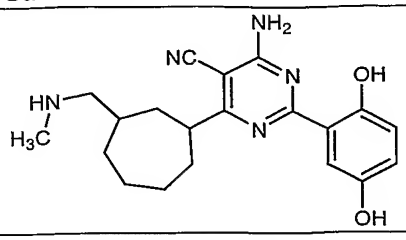
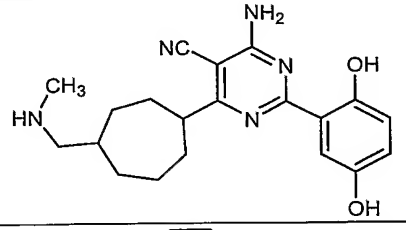
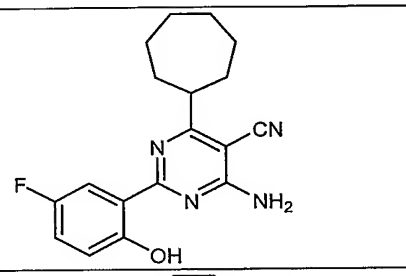
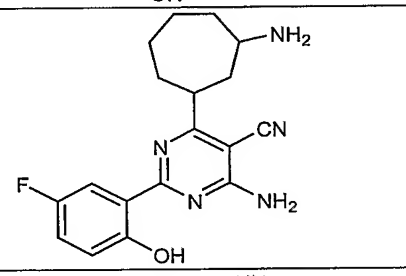
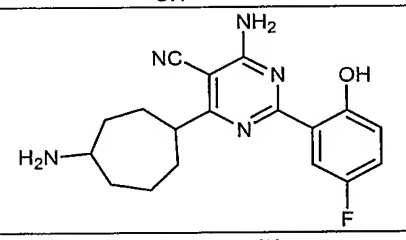
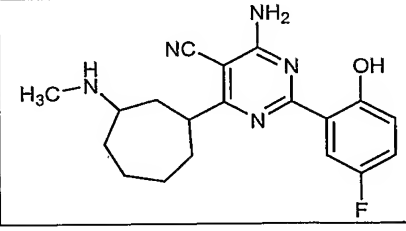
Name	Structure
4-amino-6-(3-aminocyclopentyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxy-5-methylphenyl)-6-(3-(methylamino)cyclopentyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cyclopentyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cyclopentyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxy-5-methylphenyl)-6-(3-((methylamino)methyl)cyclopentyl)pyrimidine-5-carbonitrile	
4-amino-6-cyclopentyl-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	

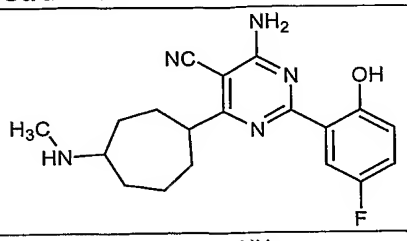
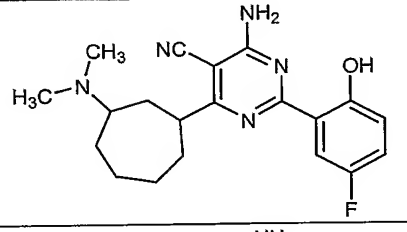
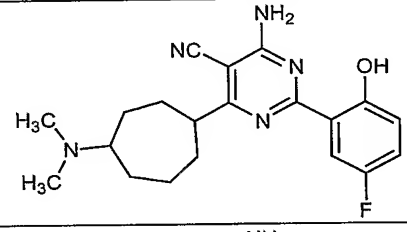
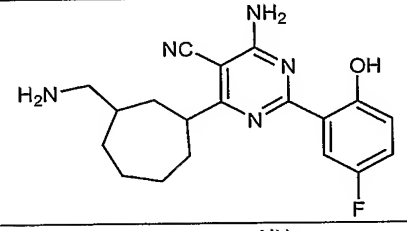
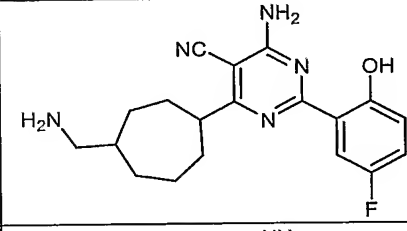
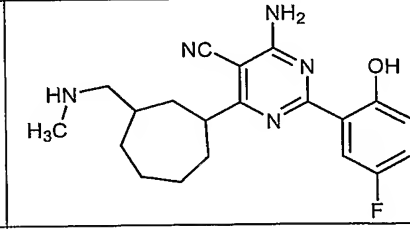
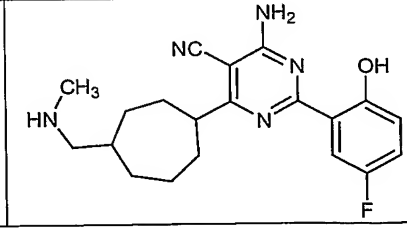
Name	Structure
4-amino-6-(3-aminocyclopentyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(3-(methylamino)cyclopentyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cyclopentyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cyclopentyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(3-((methylamino)methyl)cyclopentyl)pyrimidine-5-carbonitrile	
4-amino-6-cycloheptyl-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	

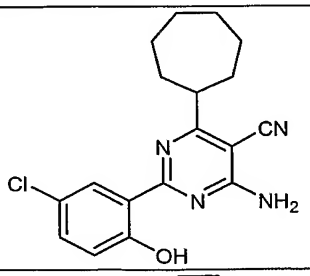
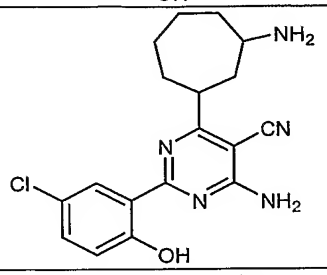
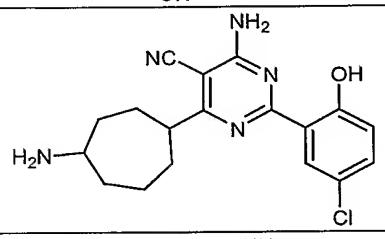
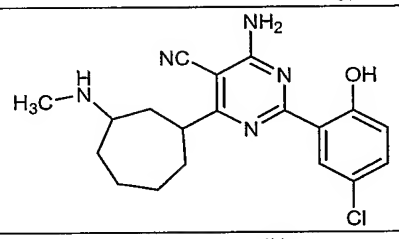
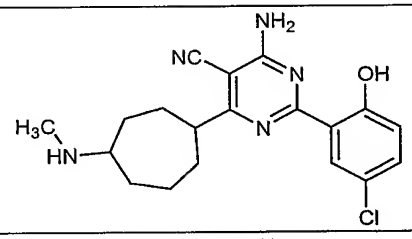
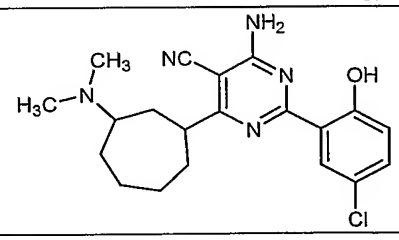
Name	Structure
4-amino-6-(3-aminocycloheptyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-aminocycloheptyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(3-(methylamino)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(4-(methylamino)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cycloheptyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(dimethylamino)cycloheptyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	

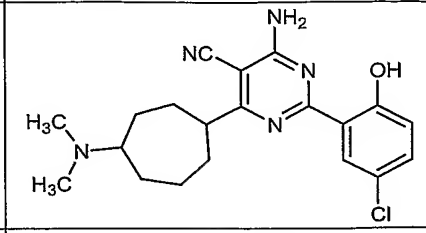
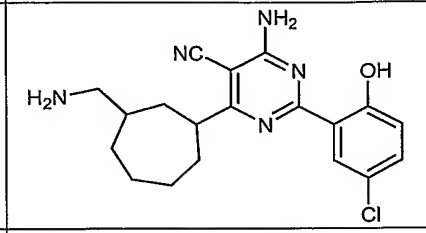
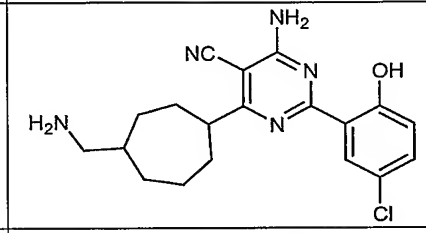
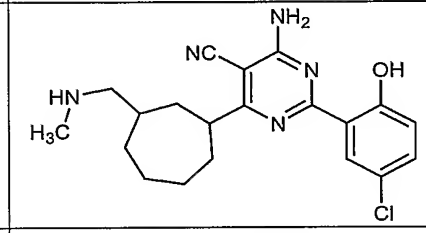
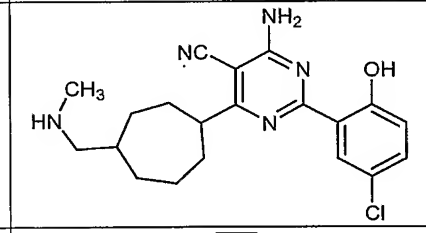
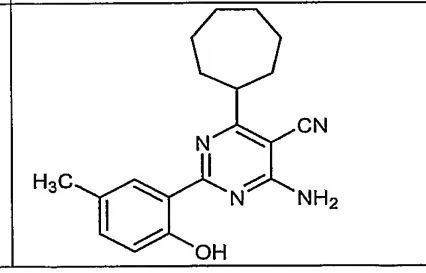
Name	Structure
4-amino-6-(3-(aminomethyl)cycloheptyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)cycloheptyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(3-((methylamino)methyl)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(4-((methylamino)methyl)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-6-cycloheptyl-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminocycloheptyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	

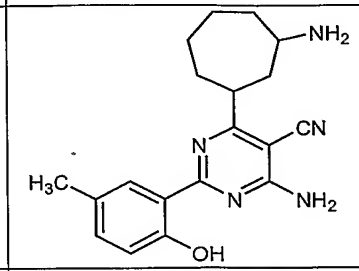
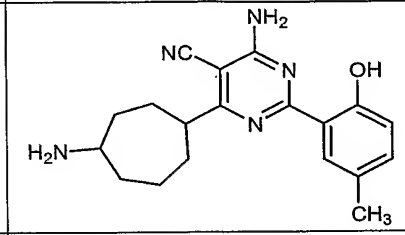
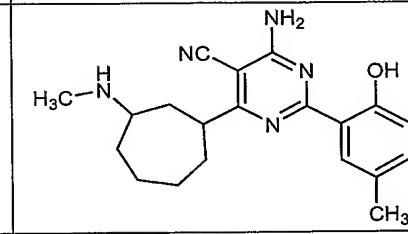
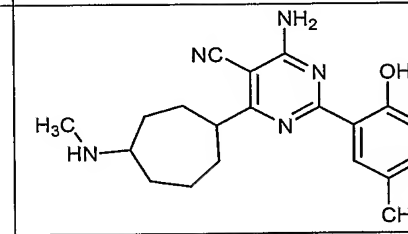
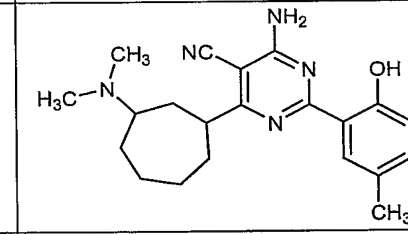
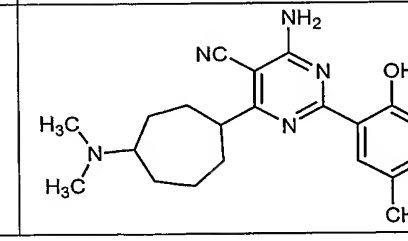
Name	Structure
4-amino-6-(4-aminocycloheptyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2,5-dihydroxyphenyl)-6-(3-(methylamino)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-2-(2,5-dihydroxyphenyl)-6-(4-(methylamino)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cycloheptyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(dimethylamino)cycloheptyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cycloheptyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)cycloheptyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	

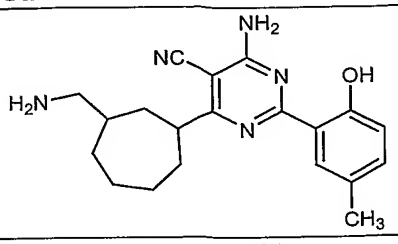
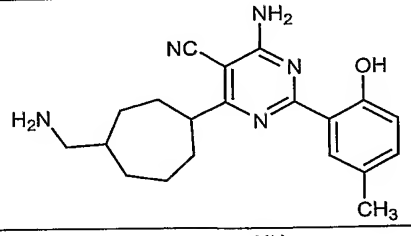
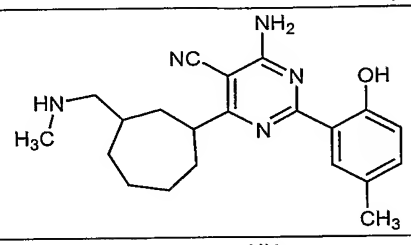
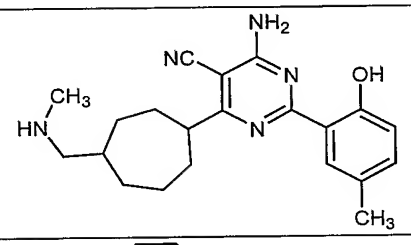
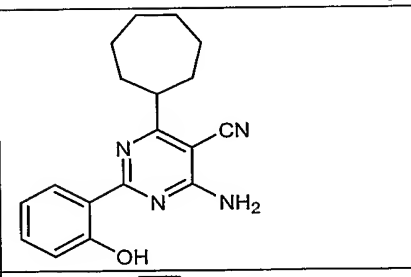
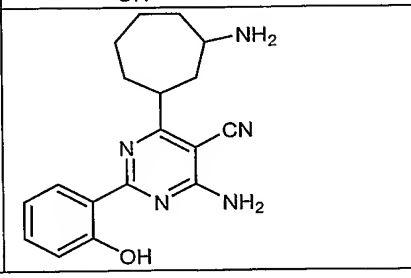
Name	Structure
4-amino-2-(2,5-dihydroxyphenyl)-6-(3-((methylamino)methyl)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-2-(2,5-dihydroxyphenyl)-6-(4-((methylamino)methyl)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-6-cycloheptyl-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminocycloheptyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-aminocycloheptyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(3-(methylamino)cycloheptyl)pyrimidine-5-carbonitrile	

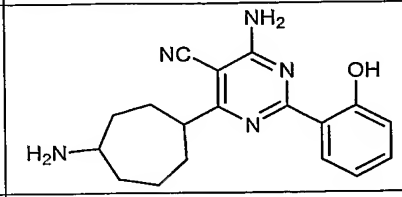
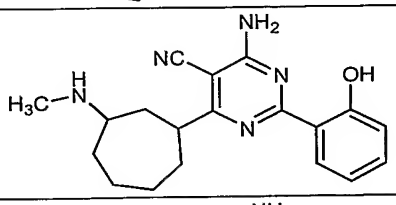
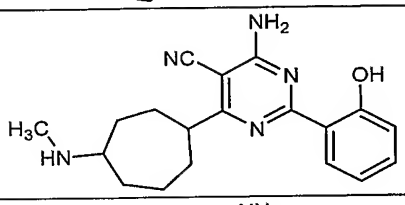
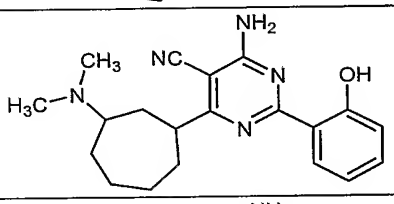
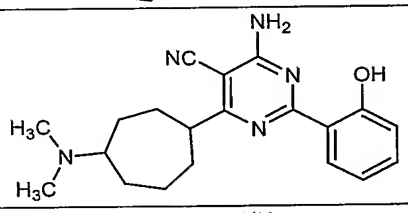
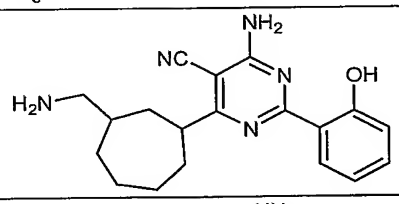
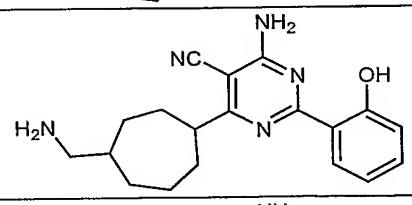
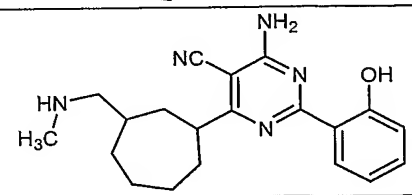
Name	Structure
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(4-(methylamino)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cycloheptyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(dimethylamino)cycloheptyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cycloheptyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)cycloheptyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(3-((methylamino)methyl)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(4-((methylamino)methyl)cycloheptyl)pyrimidine-5-carbonitrile	

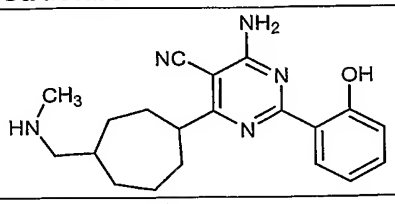
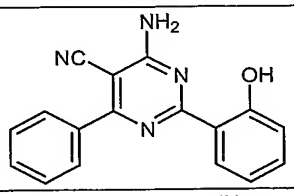
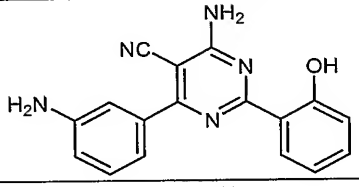
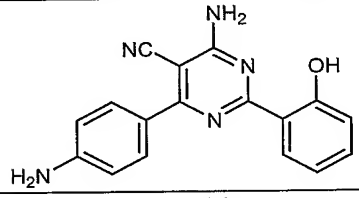
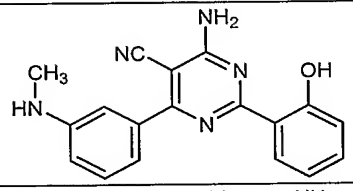
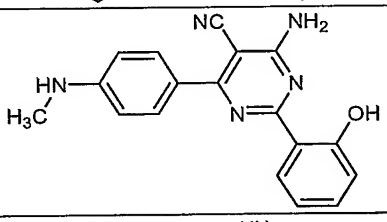
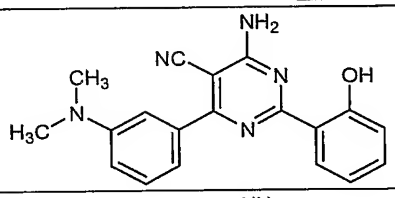
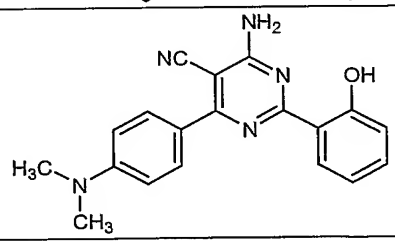
Name	Structure
4-amino-6-cycloheptyl-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminocycloheptyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-aminocycloheptyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(3-(methylamino)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(4-(methylamino)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cycloheptyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	

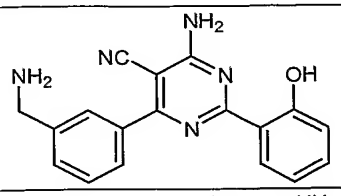
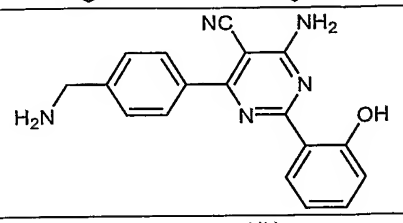
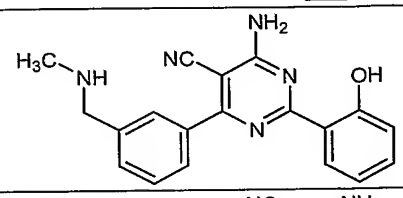
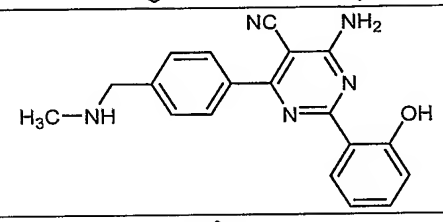
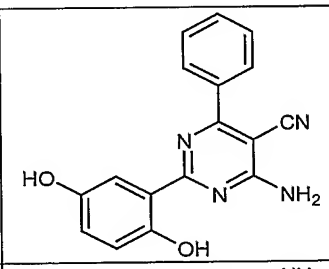
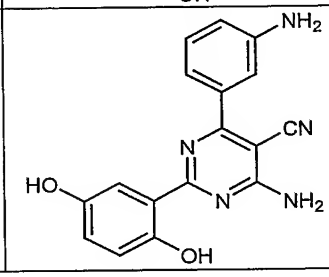
Name	Structure
4-amino-6-(4-(dimethylamino)cycloheptyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cycloheptyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)cycloheptyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(3-((methylamino)methyl)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(4-((methylamino)methyl)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-6-cycloheptyl-2-(5-methyl-2-hydroxyphenyl)pyrimidine-5-carbonitrile	

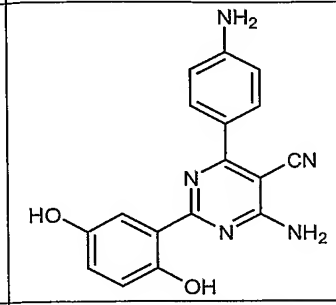
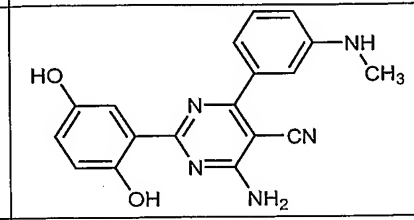
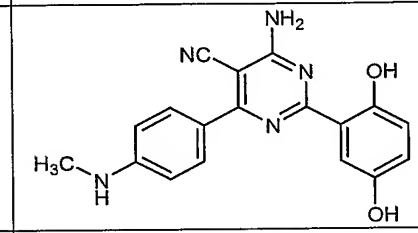
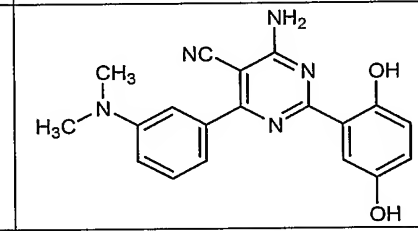
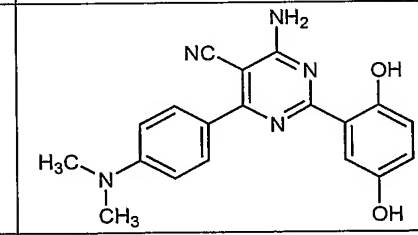
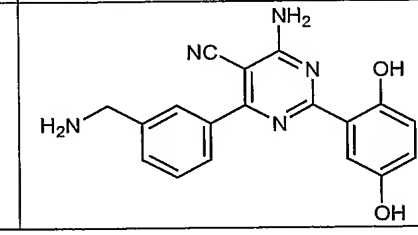
Name	Structure
4-amino-6-(3-aminocycloheptyl)-2-(5-methyl-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-aminocycloheptyl)-2-(5-methyl-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-methyl-2-hydroxyphenyl)-6-(3-(methylamino)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-methyl-2-hydroxyphenyl)-6-(4-(methylamino)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cycloheptyl)-2-(5-methyl-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(dimethylamino)cycloheptyl)-2-(5-methyl-2-hydroxyphenyl)pyrimidine-5-carbonitrile	

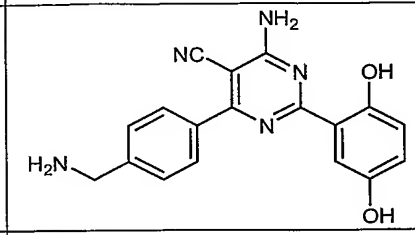
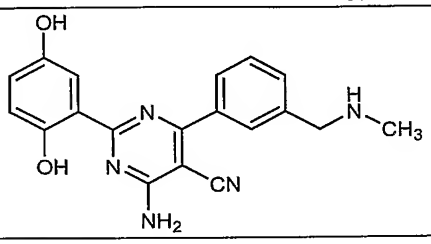
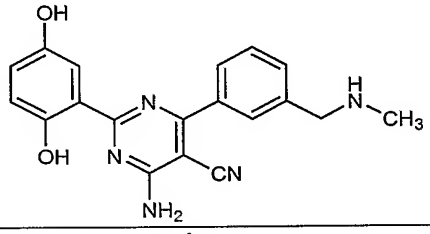
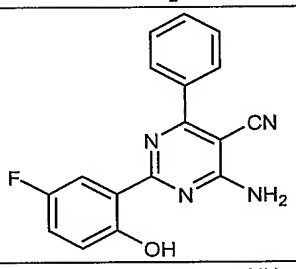
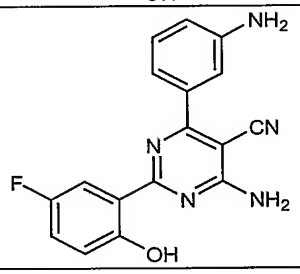
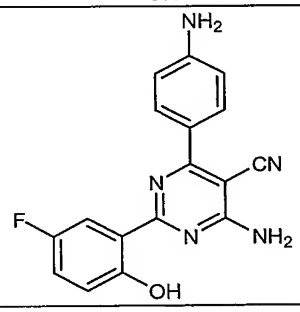
Name	Structure
4-amino-6-(3-(aminomethyl)cycloheptyl)-2-(5-methyl-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)cycloheptyl)-2-(5-methyl-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-methyl-2-hydroxyphenyl)-6-(3-((methylamino)methyl)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-methyl-2-hydroxyphenyl)-6-(4-((methylamino)methyl)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-6-cycloheptyl-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminocycloheptyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	

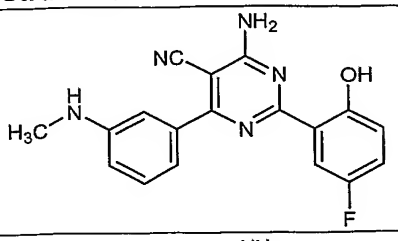
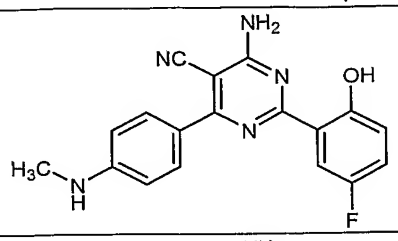
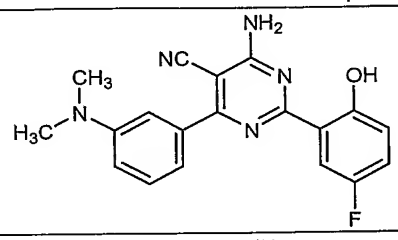
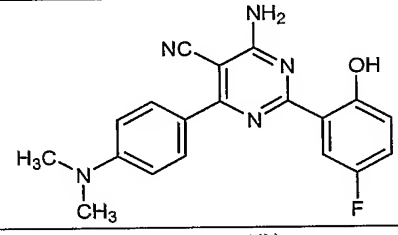
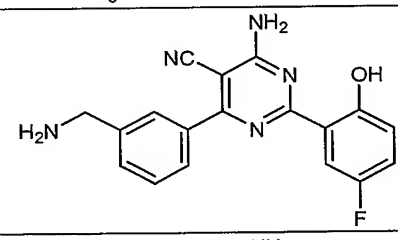
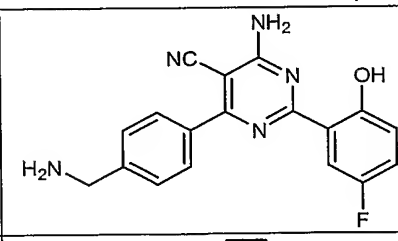
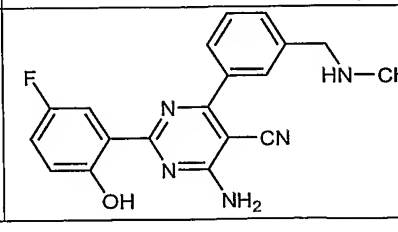
Name	Structure
4-amino-6-(4-aminocycloheptyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxyphenyl)-6-(3-(methylamino)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxyphenyl)-6-(4-(methylamino)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)cycloheptyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(dimethylamino)cycloheptyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)cycloheptyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)cycloheptyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxyphenyl)-6-(3-((methylamino)methyl)cycloheptyl)pyrimidine-5-carbonitrile	

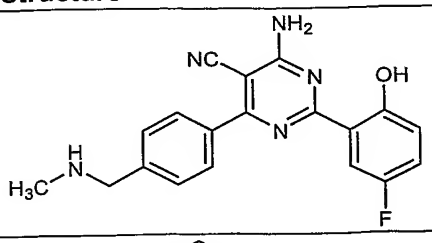
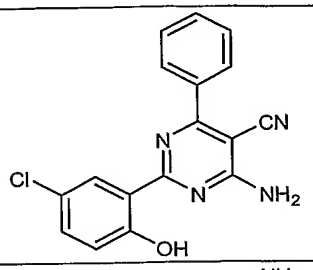
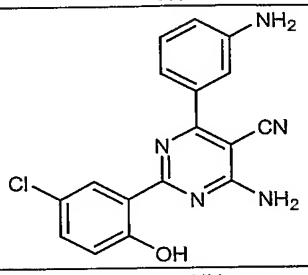
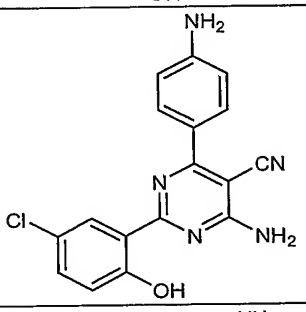
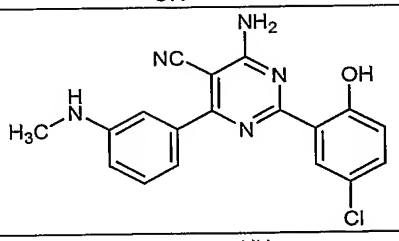
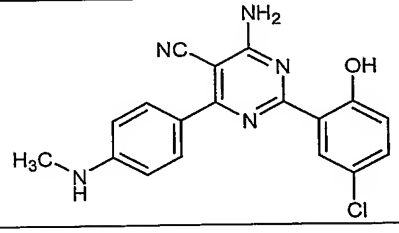
Name	Structure
4-amino-2-(5-methyl-2-hydroxyphenyl)-6-(4-((methylamino)methyl)cycloheptyl)pyrimidine-5-carbonitrile	
4-amino-6-phenyl-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminophenyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-aminophenyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxyphenyl)-6-(3-(methylamino)phenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxyphenyl)-6-(4-(methylamino)phenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)phenyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(dimethylamino)phenyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	

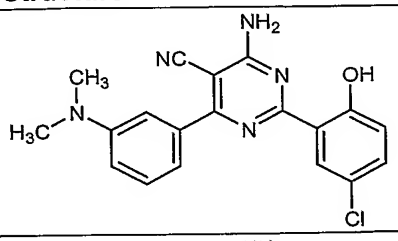
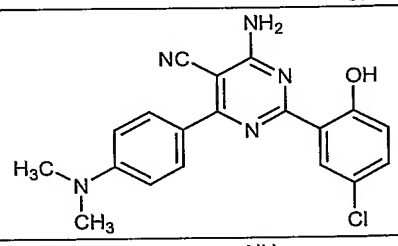
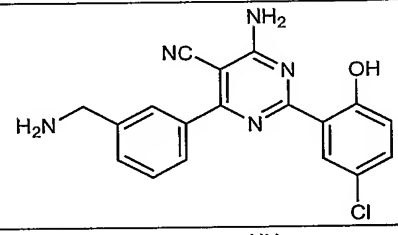
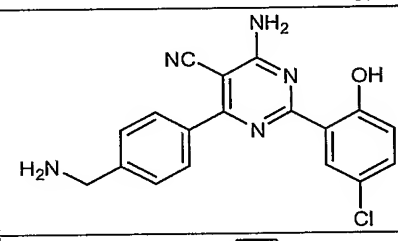
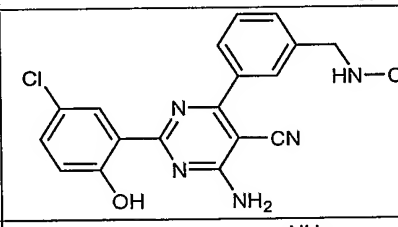
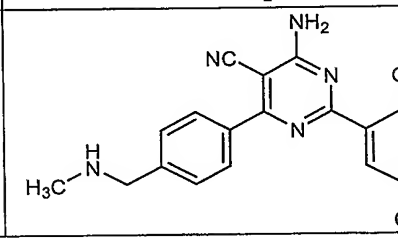
Name	Structure
4-amino-6-(3-(aminomethyl)phenyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)phenyl)-2-(2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxyphenyl)-6-(3-((methylamino)methyl)phenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxyphenyl)-6-(4-((methylamino)methyl)phenyl)pyrimidine-5-carbonitrile	
4-amino-6-phenyl-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminophenyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	

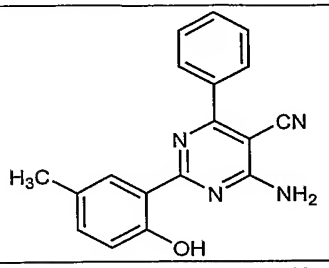
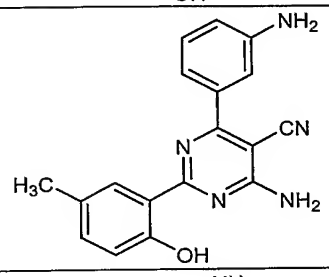
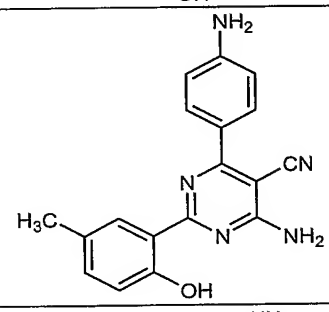
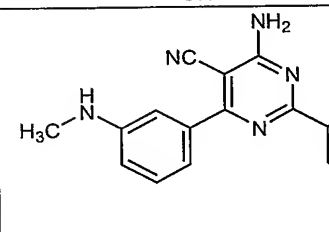
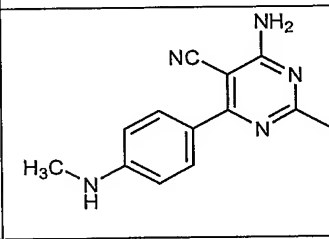
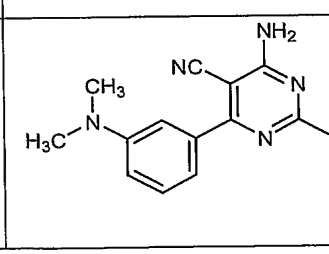
Name	Structure
4-amino-6-(4-aminophenyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2,5-dihydroxyphenyl)-6-(3-(methylamino)phenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2,5-dihydroxyphenyl)-6-(4-(methylamino)phenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)phenyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(dimethylamino)phenyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)phenyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	

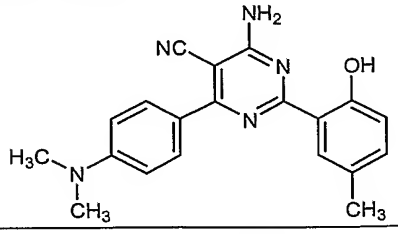
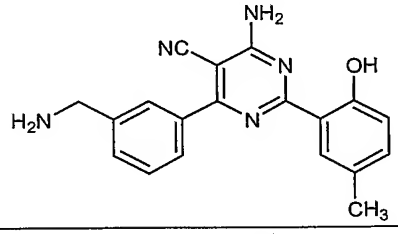
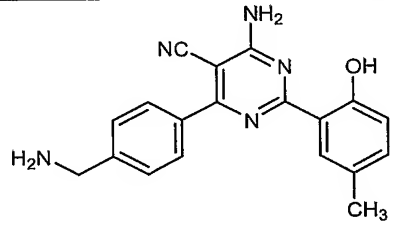
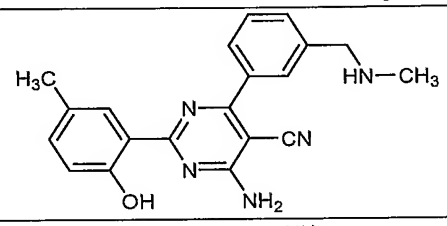
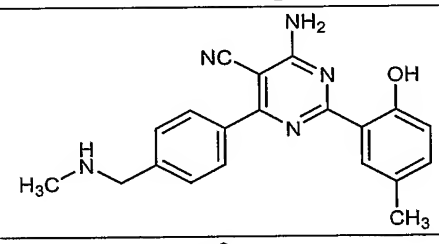
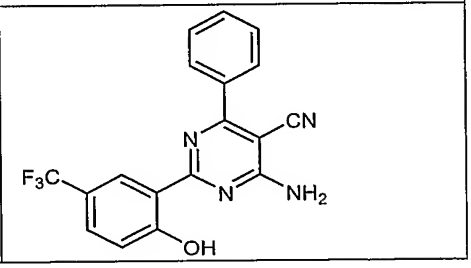
Name	Structure
4-amino-6-(4-(aminomethyl)phenyl)-2-(2,5-dihydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2,5-dihydroxyphenyl)-6-(3-((methylamino)methyl)phenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2,5-dihydroxyphenyl)-6-(4-((methylamino)methyl)phenyl)pyrimidine-5-carbonitrile	
4-amino-6-phenyl-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminophenyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-aminophenyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	

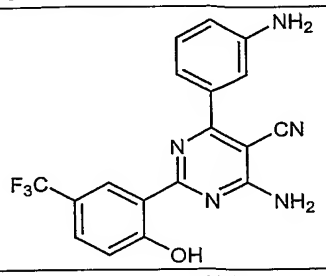
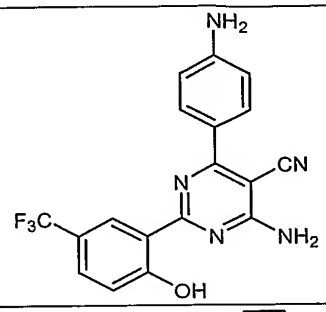
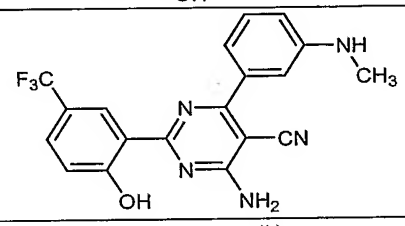
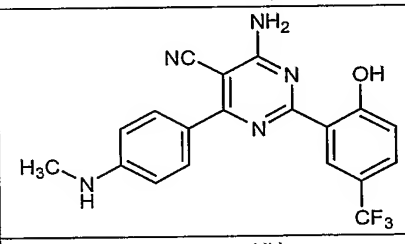
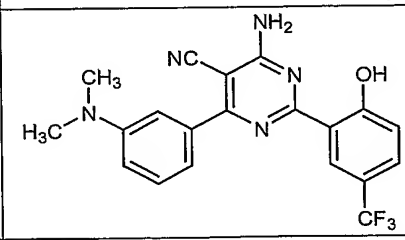
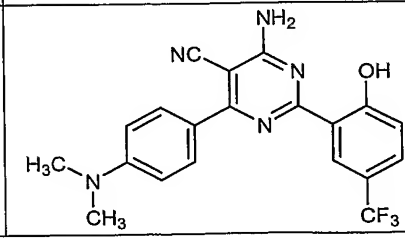
Name	Structure
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(3-(methylamino)phenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(4-(methylamino)phenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)phenyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(dimethylamino)phenyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)phenyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)phenyl)-2-(5-fluoro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(3-((methylamino)methyl)phenyl)pyrimidine-5-carbonitrile	

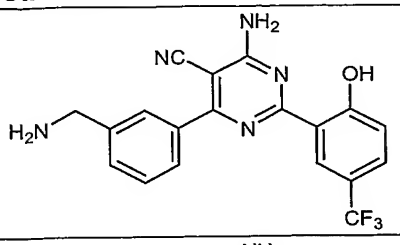
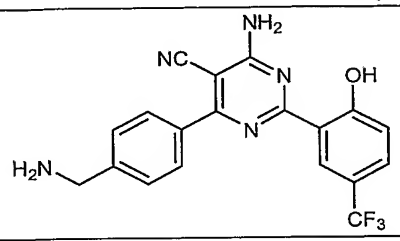
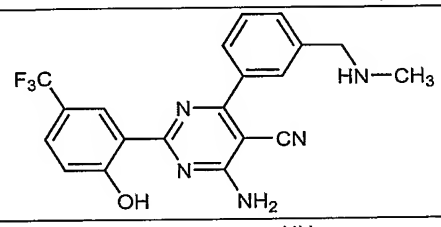
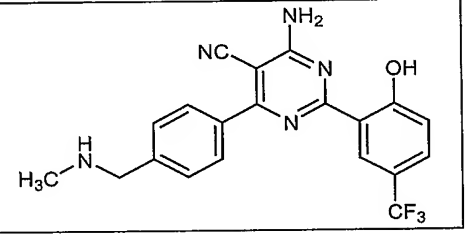
Name	Structure
4-amino-2-(5-fluoro-2-hydroxyphenyl)-6-(4-((methylamino)methyl)phenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-phenylpyrimidine-5-carbonitrile	
4-amino-6-(3-aminophenyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-aminophenyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(3-(methylamino)phenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(4-(methylamino)phenyl)pyrimidine-5-carbonitrile	

Name	Structure
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(3-(dimethylamino)phenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(4-(dimethylamino)phenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)phenyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)phenyl)-2-(5-chloro-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(3-((methylamino)methyl)phenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(4-((methylamino)methyl)phenyl)pyrimidine-5-carbonitrile	

Name	Structure
4-amino-6-phenyl-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-aminophenyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-aminophenyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxy-5-methylphenyl)-6-(3-(methylamino)phenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxy-5-methylphenyl)-6-(4-(methylamino)phenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)phenyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	

Name	Structure
4-amino-6-(4-(dimethylamino)phenyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(aminomethyl)phenyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)phenyl)-2-(2-hydroxy-5-methylphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxy-5-methylphenyl)-6-(3-((methylamino)methyl)phenyl)pyrimidine-5-carbonitrile	
4-amino-2-(2-hydroxy-5-methylphenyl)-6-(4-((methylamino)methyl)phenyl)pyrimidine-5-carbonitrile	
4-amino-6-phenyl-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	

Name	Structure
4-amino-6-(3-aminophenyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-aminophenyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(3-(methylamino)phenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(4-(methylamino)phenyl)pyrimidine-5-carbonitrile	
4-amino-6-(3-(dimethylamino)phenyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(dimethylamino)phenyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	

Name	Structure
4-amino-6-(3-(aminomethyl)phenyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-6-(4-(aminomethyl)phenyl)-2-(5-(trifluoromethyl)-2-hydroxyphenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(3-((methylamino)methyl)phenyl)pyrimidine-5-carbonitrile	
4-amino-2-(5-(trifluoromethyl)-2-hydroxyphenyl)-6-(4-((methylamino)methyl)phenyl)pyrimidine-5-carbonitrile	

DEFINITIONS

[00132] The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH_2-) radical.

[00133] The term "halo" denotes halogen atoms such as fluorine, chlorine, bromine, or iodine.

[00134] The term "carbonyl", whether used alone or with other terms such as "alkylcarbonyl", denotes -(C=O)-.

[00135] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes -CO_2H.

[00136] The term "sulfonyl," whether used alone or linked to other terms such as alkylsulfonyl, denotes the divalent radical $-SO_2-$.

[00137] The term "amido" when used by itself or with other terms such as "amidoalkyl", "N-monoalkylamido", "N-monoarylamido", "N,N-dialkylamido", "N-alkyl-N-arylamido", "N-alkyl-N-hydroxyamido" and "N-alkyl-N-hydroxyamidoalkyl", embraces a carbonyl radical substituted with an amino radical.

[00138] The terms "N-alkylamido" and "N,N-dialkylamido" denote amido groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively.

[00139] The terms "N-monoarylamido" and "N-alkyl-N-arylamido" denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical.

[00140] The term "N-alkyl-N-hydroxyamido" embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical.

[00141] The terms "sulfamyl" or "sulfonamidyl" denotes a sulfonyl radical substituted with an amino radical, forming a sulfonamide ($-SO_2NH_2$). The amino radical may be substituted with alkyl and/or aryl moieties to form, e.g., "N-alkylsulfamyl", "N-arylsulfamyl", "N,N-dialkylsulfamyl," and "N-alkyl-N-arylsulfamyl" radicals.

[00142] The term "amidino" denotes a $-C(=NH)NH_2$ radical.

[00143] The term "cyanoamidino" denotes a $-C(=N-CN)NH_2$ radical.

[00144] The term "alkyl," used alone or within other terms such as "haloalkyl" and "alkylsulfonyl," embraces linear or branched radicals having one to about twenty carbon atoms. More preferred are "lower alkyl" radicals having one to about eight carbon atoms. Examples of alkyl radicals include methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including n-butyl, isobutyl, sec-butyl, and t-butyl), pentyl (including n-pentyl and isoamyl), hexyl, octyl and the like.

[00145] The term "cycloalkyl" embraces radicals having three to ten carbon atoms, and includes monocyclic, bicyclic, and tricyclic radicals. Examples of cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, decahydronaphthyl, octahydroindyl, octahydropentalene, bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, and bicyclo[4.2.2]decyl.

[00146] The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an alkylcarbonyl radical is acetyl.

[00147] The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of an alkylthio radical is methylthio (CH_3S-).

[00148] The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. An example of an alkylsulfinyl radical is methylsulfinyl ($CH_3S(=O)$-).

[00149] The term "alkylsulfonyl" embraces alkyl radicals as defined above attached to a divalent sulfonyl radical, $-SO_2-$.

[00150] The term "amidoalkyl" embraces alkyl radicals substituted with amido radicals.

[00151] The term "N-alkyl-N-hydroxyamidoalkyl" embraces alkyl radicals substituted with an N-alkyl-N-hydroxyamido radical.

[00152] The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals.

[00153] The term "carboxyalkyl" embraces radicals having a carboxyl moiety attached to an alkyl radical.

[00154] The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihaloalkyl radicals may have two of the same halo atoms or a combination of different halo radicals; polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals.

[00155] The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms, any of which may be substituted with one or more hydroxyl radicals.

[00156] The terms "N-alkylamino" and "N, N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively.

[00157] The term "alkoxy" embraces linear or branched oxy-containing alkyl radicals having one to about ten carbon atoms. Examples of "alkoxy" radicals include methoxy and butoxy.

[00158] The term "alkoxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms substituted by one or more alkoxy radicals each having one to about ten carbon atoms.

[00159] "Alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals.

[00160] The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Examples of such alkoxycarbonyl radicals include methoxycarbonyl and t-butoxycarbonyl.

[00161] The term "alkoxycarbonylalkyl" embraces radicals having alkoxycarbonyl moiety, as defined above substituted to an alkyl radical.

Examples of such alkoxycarbonylalkyl radicals include methoxycarbonylethyl ($-(CH_2)_2(O=)COCH_3$) and t-butoxycarbonylethyl ($-(CH_2)_2(O=)COC(CH_3)_3$).

[00162] The term "alkylaminoalkyl" embraces aminoalkyl radicals wherein the nitrogen atom is substituted with an alkyl radical.

[00163] The term "alkylcarbonylalkyl" denotes an alkyl radical substituted with an "alkylcarbonyl" radical.

[00164] The term "alkenyl," used alone or within other terms such as "haloalkenyl," embraces unsaturated linear or branched radicals having two to about twenty carbon atoms and containing at least one carbon-carbon double bond. Examples of alkenyl radicals include ethenyl, propenyl butenyl, pentenyl, and the like.

[00165] The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms and containing at least one carbon-carbon double bond, and includes monocyclic, bicyclic, and tricyclic radicals. Examples of cycloalkenyl radicals include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, decahydronaphthenyl, hexahydroindenyl, hexahydropentalenyl, bicyclo[2.1.0]pentenyl, bicyclo[1.1.1]pentenyl, bicyclo[2.1.1]hexenyl, bicyclo[2.2.1]heptenyl, bicyclo[3.1.1]heptenyl, bicyclo[3.2.1]octenyl, bicyclo[2.2.2]octenyl, and bicyclo[4.2.2]decenyl.

[00166] The term "alkynyl," used alone or within other terms such as "haloalkynyl," embraces unsaturated linear or branched radicals having two to about twenty carbon atoms and containing at least one carbon-carbon triple bond. Examples of alkynyl radicals include ethynyl, propynyl butynyl, pentynyl, and the like.

[00167] The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two, or three rings wherein at least one of the rings is aromatic, and wherein such rings may be attached together in a pendant manner or may be fused. Examples of aryl radicals include phenyl, naphthyl, tetrahydronapthyl, indyl, and biphenyl. Aryl moieties, alone or in

combination, may be optionally substituted by one or more substituents selected from the group consisting of amino, halo, cyano, hydroxyl, alkyl, alkoxy, and carboxyl.

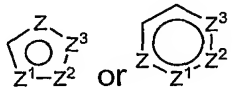
[00168] The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, and diphenethyl.

[00169] The term "arylsulfonyl" embraces aryl radicals as defined above attached to a sulfonyl radical.

[00170] The term "acyl," whether used alone or within a term such as "acylamino," denotes a radical provided by the residue after removal of hydroxyl from an organic acid.

[00171] The term "acylamino" embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino ($CH_3C(=O)NH$-).

[00172] The term "heterocyclic" or "heterocycle" means a saturated or unsaturated mono- or multi-ring carbocyclic system wherein one or more carbon atoms in the system are replaced by nitrogen, sulfur, phosphorous, and/or oxygen. The term "heterocyclic" embraces "heteroaryl" groups, which means a carbocyclic aromatic system containing one, two, or three rings wherein at least one of the rings is aromatic, wherein such rings may be attached together in a pendant manner or may be fused, and wherein one or more carbon atoms in the system are replaced by nitrogen, sulfur, phosphorous, and/or oxygen. "Heterocyclic" includes, for example, the following structures:

[00173]  or

[00174] wherein Z, Z^1, Z^2, and Z^3 are independently carbon, sulfur, phosphorous, oxygen, or nitrogen, with the proviso that one of Z, Z^1, Z^2, or Z^3 is other than carbon, but is not oxygen or sulfur when attached to another Z atom by a double bond or when attached to another oxygen or sulfur atom.

Furthermore, the optional substituents are understood to be attached to Z, Z^1, Z^2, or Z^3 only when each is carbon. For example, the term "heterocyclyl" embraces each of the following groups, although this listing is not meant to limit the definition to these groups only: furanyl; thienyl; pyrrolyl; 2-isopyrrolyl; 3-isopyrrolyl; pyrazolyl; 2-isoimidazolyl; 1,2,3-triazolyl; 1,2,4-triazolyl; 1,2-dithiolyl; 1,3-dithiolyl; 1,2,3-oxathiolyl; isoxazolyl; oxazolyl; thiazolyl; isothiazolyl; 1,2,3-oxadiazolyl; 1,2,4-oxadiazolyl; 1,2,5-oxadiazolyl; 1,3,4-oxadiazolyl; 1,2,3,4-oxatriazolyl; 1,2,3,5-oxatriazolyl; 1,2,3-dioxazolyl; 1,2,4-dioxazolyl; 1,3,2-dioxazolyl; 1,3,4-dioxazolyl; 1,2,5-oxathiazolyl; 1,3-oxathiolyl; 1,2-pyranyl; 1,4-pyranyl; 1,2-pyranonyl; 1,4-pyranonyl; 1,2-dioxinyl; 1,3-dioxinyl; pyridyl; pyridazyl; pyrimidyl; pyrazinyl; piperazyl; 1,3,5-triazinyl; 1,2,4-triazinyl; 1,2,3-triazinyl; 1,2,4-oxazinyl; 1,3,2-oxazinyl; 1,3,6-oxazinyl; 1,2,6-oxazinyl; 1,4-oxazinyl; o-isoxazinyl; p-isoxazinyl; 1,2,5-oxathiazinyl; 1,4-oxazinyl; o-isoxazinyl; p-isoxazinyl; 1,2,5-oxathiainzyl; 1,2,6-oxathiainzyl; 1,4,2-oxadiainzyl; 1,3,5,2-oxadiainzyl; morpholino; azepinyl; oxepinyl; thiepinyl; 1,2,4-diazepinyl; benzofuranyl; isobenzofuranyl; benzothiofuranyl; isobenzothiofuranyl; indolyl; indoleninyl; 2-isobenzazolyl; 1,5-pyrindinyl; pyrano[3,4-b]pyrrolyl; isoindazolyl; indoxazinyl; benzoxazolyl; anthranilyl; 1,2-benzopyranyl; quinolyl; isoquinolyl; cinnolyl; quinazolyl; naphthyridyl; pyrido[3,4-b]pyridyl; pyrido[3,2-b]pyridyl; pyrido[4,3-b]pyridyl; 1,3,2-benzoxazyl; 1,4,2-benzoxazyl; 2,1,3-benzoxazyl; 3,1,4-benzoxazyl; 1,2-benzoisoxazyl; 1,4-benzoisoxazyl; carbazolyl; xanthenyl; acridinyl; purinyl; thiazolidyl; piperidyl; pyrrolidyl; 1,2-dihydroazinyl; 1,4-dihydroazinyl; 1,2,3,6-tetrahydro-1,3-diazinyl; perhydro-1,4-diazinyl; 1,2-thiapyranyl; and 1,4-thiapyranyl. Heterocyclic moieties, alone or in combination, may be optionally substituted by one or more substituents selected from the group consisting of amino, halo, cyano, hydroxyl, alkyl, alkoxy, and carboxyl.

[00175] The term "heteroaryl" also embraces radicals where heterocyclic radicals are fused with aryl radicals as defined herein. Examples

of such fused bicyclic radicals include benzofuran, benzothiophene, and the like.

[00176] The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl.

[00177] The terms benzyl and phenylmethyl are interchangeable.

[00178] The phrases "combination therapy", "co-administration", "administration with", or "co-therapy", in defining the use of a selective IKK-2 inhibitory agent in combination with another therapeutic agent such as another analgesic agent, is intended to embrace administration of each agent in a sequential manner in a regimen that may provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule or dosage device having a fixed ratio of these active agents or in multiple, separate capsules or dosage devices for each agent, where the separate capsules or dosage devices can be taken together contemporaneously, or taken within a period of time sufficient to receive a beneficial effect from both of the constituent agents of the combination.

[00179] The term "subject" for purposes of treatment includes any human or animal subject who is in need of the prevention of, or who has pain, inflammation and/or any one of the known inflammation-associated disorders. The subject is typically a human subject.

[00180] The phrase "therapeutic combination" as used herein refers to the combination of two or more therapeutic compounds and, optionally, one or more pharmaceutically acceptable carrier used to provide dosage forms that produce a beneficial effect of each therapeutic compound in the subject at the desired time, whether the therapeutic compounds are administered substantially simultaneously, or sequentially.

[00181] The phrase "therapeutically effective" as used herein refers to an amount of a therapeutic compound, or amounts of combined therapeutic

compounds in combination therapy. The amount or combined amounts achieve one or more of the goals of preventing, inhibiting, reducing or eliminating the inflammation or inflammation-related disease or condition. A "therapeutically-effective" amount of each agent in a combination therapy is expected to be less than an amount used in treatment using agent by itself, thus while avoiding adverse side effects typically associated with alternative therapies, namely higher dose monotherapy of each agent by itself.

[00182] The terms "treating" or "to treat" means to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms in a subject. The term "treatment" includes alleviation, elimination of causation of or prevention of pain and/or inflammation associated with, but not limited to, any of the diseases or disorders described above.

[00183] Pharmaceutically acceptable salts of the compounds of Formula I include the acid addition and base salts thereof.

[00184] Suitable acid addition salts are formed from acids that form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

[00185] Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

[00186] Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

[00187] Pharmaceutically acceptable salts of compounds of Formula I may be prepared by one or more of three methods: (i) by reacting the compound of Formula I with the desired acid or base; (ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of Formula I or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or (iii) by converting one salt of the compound of Formula I to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column. All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the resulting salt may vary from completely ionized to almost non-ionized.

[00188] The compounds of the invention may exist in both unsolvated and solvated forms. The term "solvate" is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term "hydrate" is employed when said solvent is water.

[00189] Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see Haleblian, J. Pharm. Sci., **64(8)**, 1269-1288 (1975).

[00190] Hereinafter all references to compounds of Formula I include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

[00191] The compounds of the invention include compounds of Formula I as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of Formula I.

[00192] As indicated, so-called prodrugs of the compounds of Formula I are also within the scope of the invention. The term "prodrug" refers to a compound that is a drug precursor which, following administration to a subject and subsequent absorption, is converted to an active species *in vivo* via some process, such as a metabolic process. Other products from the conversion process are easily disposed of by the body. The more preferred prodrugs are those involving a conversion process that produces products that are generally accepted as safe.

[00193] Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of Formula I with certain moieties known to those skilled in the art as "pro-moieties."

[00194] Some examples of prodrugs in accordance with the invention include: (i) where the compound of Formula I contains a carboxylic acid functionality (-CO_2H), an ester thereof, for example, a compound wherein the hydrogen of the carboxylic acid functionality of the compound of Formula I is replaced by C_1-C_8 alkyl; (ii) where the compound of Formula I contains an alcohol functionality (-OH), an ether thereof, for example, a compound wherein the hydrogen of the alcohol functionality of the compound of Formula I is replaced by C_1-C_6 alkanoyloxymethyl; and (iii) where the compound of Formula I contains a primary or secondary amino functionality (-NH_2 or -NHR where R ≠

H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound of Formula I is/are replaced by C_1-C_{10} alkanoyl.

[00195] Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

[00196] Moreover, certain compounds of Formula I may themselves act as prodrugs of other compounds of Formula I.

[00197] Also included within the scope of the invention are metabolites of compounds of Formula I, that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the invention include: (i) where the compound of Formula I contains a methyl group, an hydroxymethyl derivative thereof ($-CH_3 \rightarrow -CH_2OH$); (ii) where the compound of Formula I contains an alkoxy group, an hydroxy derivative thereof ($-OR \rightarrow -OH$); (iii) where the compound of Formula I contains a tertiary amino group, a secondary amino derivative thereof ($-NR^aR^b \rightarrow -NHR^a$ or $-NHR^b$); (iv) where the compound of Formula I contains a secondary amino group, a primary derivative thereof ($-NHR \rightarrow -NH_2$); (v) where the compound of Formula I contains a phenyl moiety, a phenol derivative thereof ($-Ph \rightarrow -PhOH$); and (vi) where the compound of Formula I contains an amide group, a carboxylic acid derivative thereof ($-CONH_2 \rightarrow -COOH$).

[00198] Compounds of Formula I containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of Formula I contains an alkenyl or alkenylene group, geometric cis/trans (or Z/E) isomers are possible. Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ("tautomerism") can occur. This can take the form of proton tautomerism in compounds of Formula I containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in

compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

[00199] Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of Formula I, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, d-lactate or l-lysine, or racemic, for example, dl-tartrate or dl-arginine.

[00200] Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization.

[00201] Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (chiral HPLC).

[00202] Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of Formula I contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

[00203] Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2 to 20%, and from 0 to 5% by

volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

[00204] Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art.

[00205] The present invention includes all pharmaceutically acceptable isotopically-labeled compounds of Formula I wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

[00206] Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

[00207] Certain isotopically-labeled compounds of Formula I, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium (^{3}H) and ^{14}C are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[00208] Substitution with heavier isotopes such as deuterium (^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

[00209] Substitution with positron-emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[00210] Isotopically-labeled compounds of Formula I can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using

an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[00211] Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone, or d_6-DMSO.

[00212] Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

[00213] Generally, the compounds of the invention may be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

[00214] The compounds of the invention may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). For example, compounds of Formula I may be used in co-therapies, partially or completely, in place of other conventional antiinflammatory therapies, such as together with other IKK-2 inhibitors, steroids, NSAIDs, COX-2 selective inhibitors, matrix metalloproteinase inhibitors, 5-lipoxygenase inhibitors, LTB_4 antagonists and LTA_4 hydrolase inhibitors.

[00215] Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art.

[00216] The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

[00217] Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays and liquid formulations.

[00218] Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

[00219] The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Liang and Chen, Expert Opinion in Therapeutic Patents, **11(6)**, 981-986 (2001).

[00220] For tablet dosage forms, depending on dose, the drug may make up from 1 to 80 wt.% of the dosage form, more typically from 5 to 60 wt.% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 to 25 wt.%, preferably from 5 to 20 wt.% of the dosage form.

[00221] Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin,

sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

[00222] Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 to 5 wt.% of the tablet, and glidants may comprise from 0.2 to 1 wt.% of the tablet.

[00223] Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 to 10 wt.%, preferably from 0.5 to 3 wt.% of the tablet.

[00224] Other possible ingredients include anti-oxidants, colorants, flavoring agents, preservatives and taste-masking agents.

[00225] Exemplary tablets contain up to about 80% drug, from about 10 to about 90 wt.% binder, from about 0 to about 85 wt.% diluent, from about 2 to about 10 wt.% disintegrant, and from about 0.25 to about 10 wt.% lubricant.

[00226] Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

[00227] Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellable thin film dosage forms which

may be rapidly dissolving or mucoadhesive and typically comprise a compound of Formula I, a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabilizer or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

[00228] The compound of Formula I may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 to 80 wt.%, more typically from 20 to 50 wt.%, of the solutes. Less soluble compounds may comprise a greater proportion of the composition, typically up to 88 wt.% of the solutes. Alternatively, the compound of Formula I may be in the form of multiparticulate beads.

[00229] The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 wt.%, more typically in the range 30 to 80 wt.%.

[00230] Other possible ingredients include anti-oxidants, colorants, flavorings and flavor enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

[00231] Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

[00232] Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted- and programmed-release.

[00233] Suitable modified release formulations for the purposes of the invention are described in U.S. Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma et al., Pharmaceutical Technology On-line,

25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in PCT Publication No. WO 00/35298.

[00234] The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

[00235] Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

[00236] The preparation of parenteral formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

[00237] The solubility of compounds of Formula I used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

[00238] Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted- and programmed-release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(dl-lactic-coglycolic)acid (PGLA) microspheres.

[00239] The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated; see, e.g., Finnin and Morgan, J Pharm Sci, **88(10)**, 955-958 (1999).

[00240] Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

[00241] Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted- and programmed-release.

[00242] The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

[00243] The pressurized container, pump, spray, atomizer, or nebulizer contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active,

a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[00244] Prior to use in a dry powder or suspension formulation, the drug product is micronized to a size suitable for delivery by inhalation (typically less than 5 μm). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

[00245] Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as l-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

[00246] A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from 1 μg to 20 mg of the compound of the invention per actuation and the actuation volume may vary from 1 to 100 μL. A typical formulation may comprise a compound of Formula I, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

[00247] Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

[00248] Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA.

Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted- and programmed-release.

[00249] In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 20 to 1000 µg of the compound of Formula I. The overall daily dose will typically be in the range 100 µg to 10 mg which may be administered in a single dose or, more usually, as divided doses throughout the day, for Step 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

[00250] The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

[00251] Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted- and programmed-release.

[00252] The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g., absorbable gel sponges, collagen) and non-biodegradable (e.g., silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated

together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

[00253] Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted- or programmed-release.

[00254] The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

[00255] Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e., as a carrier, diluent, or solubilizer. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, such as those described in PCT Publication No. WO 98/55148.

[00256] Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

[00257] Such kits comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of Formula I in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An

example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

[00258] Such kits are particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

[00259] The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the inflammation or inflammation related disorder, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 1000 mg, preferably in the range of about 7.0 to 350 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 0.5 to 30 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day. In the case of skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

[00260] It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

[00261] These dosages are based on an average human subject having a weight of about 60 to 70 kg. The physician will readily be able to

determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

[00262] For the avoidance of doubt, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

[00263] "DMF" is N,N-dimethylformamide.

[00264] "DMSO" is dimethylsulfoxide.

[00265] "ESI" is electrospray ionization Mass spectrometry.

[00266] "NMR" is nuclear magnetic resonance.

[00267] "Ph" is phenyl.

[00268] "EtOAc" is ethyl acetate.

[00269] "Boc" is t-butoxycarbonyl.

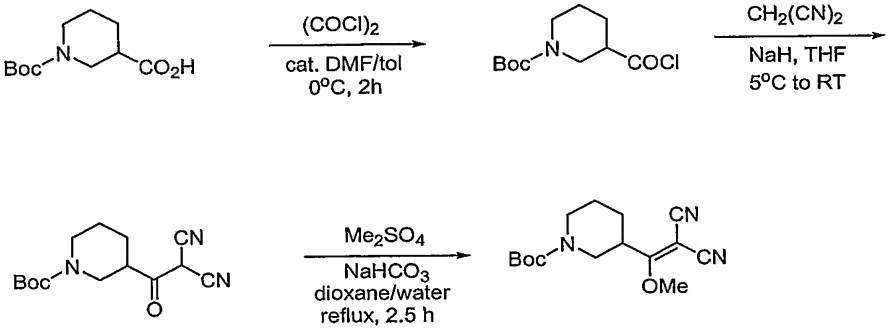
[00270] "dppf" is bis(diphenylphosphino)ferrocene.

REACTION SCHEMES

[00271] The compounds of the invention can be synthesized according to the following procedures of Scheme I and II, wherein the R substituents are as defined for Formula I and II, except where further noted.

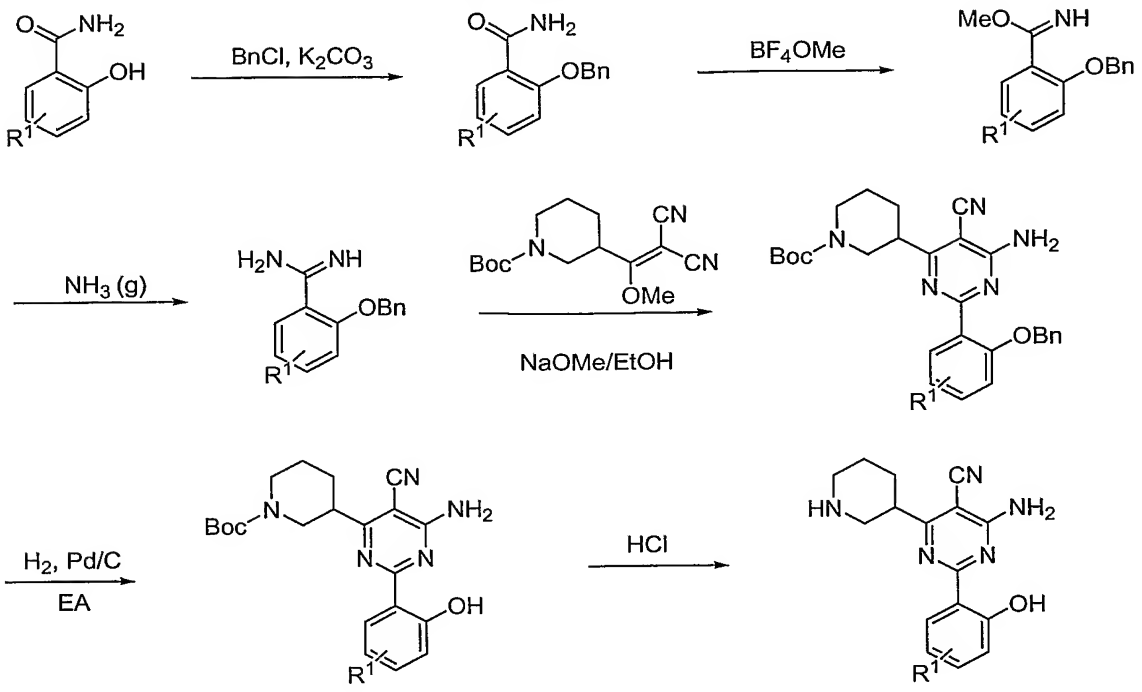
SCHEME I

Synthesis of tert-butyl 3-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate



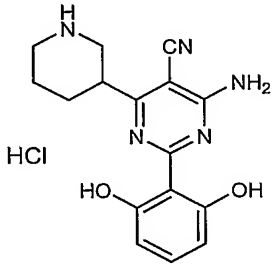
SCHEME II

Synthesis of substituted pyrimidines



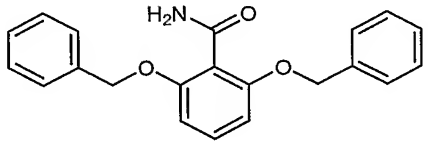
5 EXAMPLES

[00272] Example 1: 4-amino-2-(2,6-dihydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride



[00273]

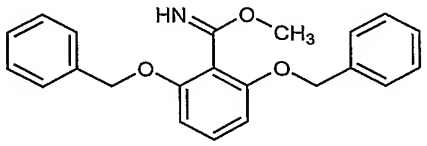
[00274] Step 1: Preparation of 2,6-bis(benzyloxy)benzamide



10 **[00275]**

[00276] To a room temperature solution of 2,6-dibenzyloxybenzonitrile (50 g, 160 mmol) in 120 mL benzyl alcohol was added 32 g of KOH and 20 mL H_2O. The resulting suspension was placed in a 130°C oil bath for 18 h. The benzyl alcohol was then removed on a rotary evaporator, and the resulting solid was slurried in 700 mL H_2O. The solid was collected and suspended in boiling diethyl ether to yield the desired product as a white solid. LC/MS m/z=334.1(m+1).

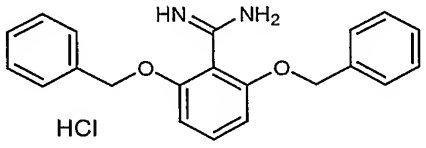
[00277] Step 2: Preparation of methyl 2,6-bis(benzyloxy)benzenecarboximidoate



[00278]

[00279] To a room temperature solution of 2,6-bis(benzyloxy)benzamide (Step 1, 24 g, 72 mmol) in 160 mL methylene chloride was added trimethyloxonium tetrafluoroborate (12.8 g, 86.4 mmol) and the resulting suspension was stirred for 4 h. The reaction was then filtered and concentrated to give a light brown semi-solid, which was used without further purification. LC/MS m/z=348.2 (m+1).

[00280] Step 3: Preparation of 2,6-bis(benzyloxy)benzenecarboximidamide hydrochloride

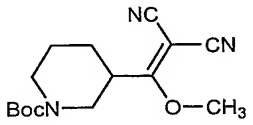


[00281]

[00282] To a solution of methyl 2,6-bis(benzyloxy)benzenecarboximidoate (Step 2, 23 g, 66 mmol) in 300 mL ethanol, was added 300 mL of condensed ammonia. The solution was sealed and heated to 80°C at 300 psi. After 40 h the reaction was cooled, filtered, and then concentrated. The resulting solid was suspended in 200 mL of 4N hydrogen chloride in 1,4-dioxane. After 1 h the suspension was concentrated

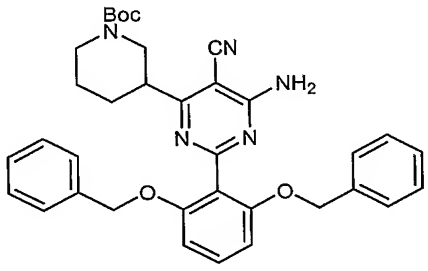
and the resulting solids were purified by reverse phase HPLC to yield the desired compound as the hydrochloride salt. LC/MS m/z=333.1 (m+1).

[00283] Step 4: Preparation of tert-butyl 3-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate

[00284] 

[00285] To a 0°C solution of Boc-piperidine carboxylic acid (100.88 g, 0.440 mol) in toluene (1 L) was added oxalylchloride (55.85 g, 0.440 mol) and a few drops of DMF. The mixture was stirred for 2 h. CH_2Cl_2 (100 mL) was added and the mixture was clarified by filtration. The filtrate was concentrated under reduced pressure to yield the acid chloride as a brown oil. NaH (14.7 g, 0.613 mol) was added to a 0°C solution of malononitrile (20.3 g, 0.307 mol) in THF (300 mL). Then the acid chloride (75.9 g) in THF (75 mL) was added. The reaction was stirred at room temperature for 1 h. Then dimethylsulfate (46.4 g, 0.368 mol) was added and the mixture was refluxed for 2.5 h After cooling to room temperature, ether (500 mL) was added and then washed with water (2 x 250 mL). The reaction mixture was dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. The material was purified by flash column chromatography to yield the title product.

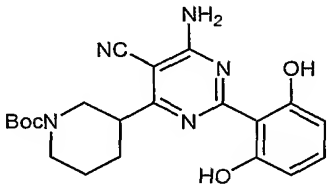
[00286] Step 5: Preparation of tert-butyl 3-{6-amino-2-[2,6-bis(benzyloxy)phenyl]-5-cyanopyrimidin-4-yl}piperidine-1-carboxylate

[00287] 

[00288] To a solution of tert-butyl 3-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate (Step 4, 3.5 g, 12 mmol) and 2,6-

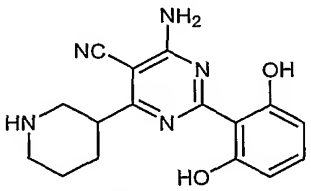
bis(benzyloxy)benzenecarboximidamide hydrochloride (Step 3, 4.4 g, 12 mmol) in 35 mL absolute ethanol, was added sodium methoxide (25% w/w solution in methanol, 6.2 mL). The solution was then heated to reflux for 3 h, then concentrated to remove the ethanol. The resulting crude material was partitioned between 100 mL ethyl acetate and 30 mL H_2O. The organic layer was dried over $MgSO_4$ and concentrated. The resulting solid was triturated with 500 mL diethyl ether, and the solids were then collected by filtration and the filtrate concentrated to give the desired compound as a yellow solid of good purity. LC/MS m/z=592.2 (m+1).

[00289] Step 6: Preparation of tert-butyl 3-[6-amino-5-cyano-2-(2,6-dihydroxyphenyl)pyrimidin-4-yl]piperidine-1-carboxylate

[00290] 

[00291] To a solution of tert-butyl 3-{6-amino-2-[2,6-bis(benzyloxy)phenyl]-5-cyanopyrimidin-4- yl}piperidine-1-carboxylate (Step 5, 2.9 g, 5 mmol) in 25 mL ethyl acetate and 5 mL glacial acetic acid was added 800 mg of 10% Palladium on carbon. The reaction was then blanketed with a hydrogen balloon and stirred for 18 h. The reaction was vented and filtered through celite. Then filtrate was concentrated and the resulting crude solid was crystallized from boiling ethanol to give the desired compound. LC/MS m/z=412.1 (m+1).

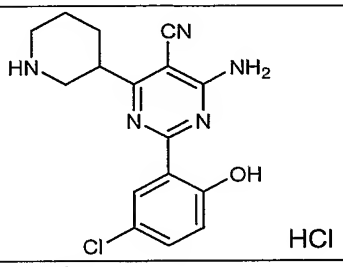
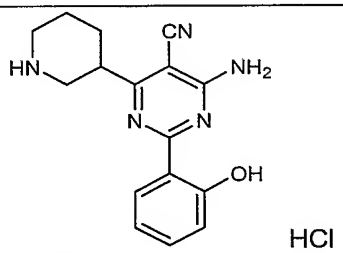
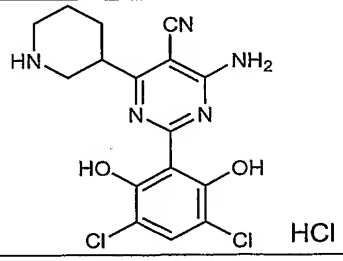
[00292] Step 7: Preparation of 4-amino-2-(2,6-dihydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride

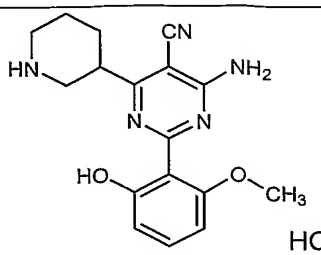
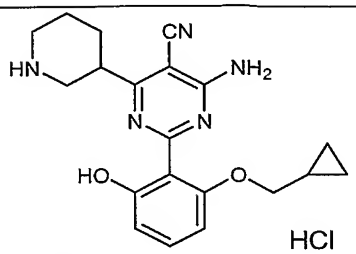
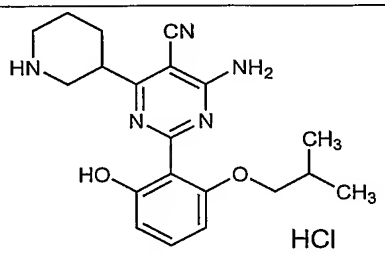
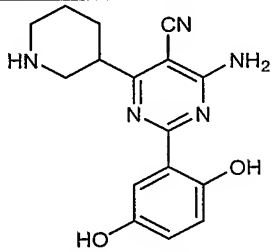
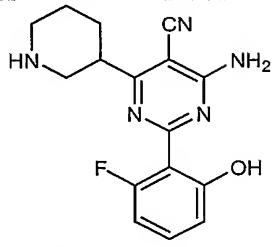
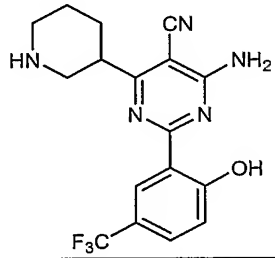
[00293] 

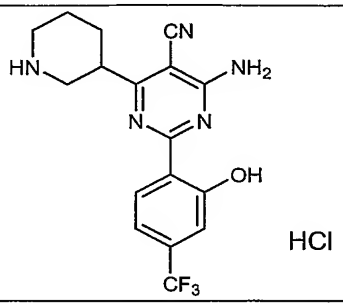
HCl

[00294] Tert-butyl 3-[6-amino-5-cyano-2-(2,6-dihydroxyphenyl)pyrimidin-4-yl]piperidine-1-carboxylate (Step 6, 180 mg, 0.4 mmol) was stirred in 3 mL of 4N hydrogen chloride in 1,4-dioxane for 1 h. The mixture was then concentrated and suspended in a boiling 1:1:1 mixture (1 mL each) of 1N hydrochloric acid, acetonitrile, and methanol. After 15 min the suspension was filtered to give the desired yellow compound as the hydrochloride salt. LC/MS m/z=312.2 (m+1).

[00295] Examples 2-12 were prepared in a similar manner.

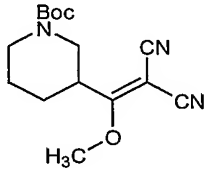
Example	Name and structure	Name and structure	Mass Spec.
3	4-amino-2-(5-chloro-2-hydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride		
4	4-amino-2-(2-hydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride		
5	4-amino-2-(3,5-dichloro-2,6-dihydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride		

Example	Name and structure	Name and structure	Mass Spec.
6	4-amino-2-(2-hydroxy-6-methoxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride		
7	4-amino-2-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride		
8	4-amino-2-(2-hydroxy-6-isobutoxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride		
9	4-amino-2-(2,5-dihydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride		
10	4-amino-2-(2-fluoro-6-hydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride		
11	4-amino-2-[2-hydroxy-5-(trifluoromethyl)phenyl]-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride		

Example	Name and structure	Name and structure	Mass Spec.
12	4-amino-2-[2-hydroxy-4-(trifluoromethyl)phenyl]-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride		

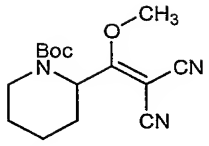
[00296] For the remaining examples, unless otherwise noted, ^{1}H NMR spectra were obtained on a Bruker AV 500 or a Bruker AV-300 spectrometer. Spectra are given in ppm (δ) and coupling constants, *J*, are reported in Hertz. Tetramethylsilane was used as an internal standard for proton spectra and the solvent peak was used as the reference peak for carbon spectra. Mass spectra were obtained on a Perkin Elmer Sciex 100 atmospheric pressure chemical ionization (APCI) mass spectrometer, or a Finnigan LCQ Duo LCMS ion trap electrospray ionization mass spectrometer. Thin-layer chromatography (TLC) was performed using Analtech silica gel plates and visualized by ultraviolet (UV) light. HPLC analyses were obtained using a Phenomenex Luna C18(2) column (150 × 4.6 mm) with UV detection at 254 nm, using aqueous TFA in acetonitrile as the eluent on a Varian Prostar HPLC. Purification using preparative HPLC was performed using a Phenomenex Luna C18(2) column (250 × 21.2 mm, 10μ) on a Varian Prostar, with UV detection at 254 nm and a concentrated aqueous solution of NH_4OH in acetonitrile as the eluent. Medium pressure column chromatographies were performed on a Biotage Horizon instrument using Biotage cartridge Si Flash 12+M, Flash 25+M or Flash 40+M, with UV detection at 254 nm. Flash chromatography column purifications were performed using silica gel 60, 230-400 mesh (E. Merck). Elemental analyses were performed by Quantitative Technologies, Inc. (Whitehouse, NJ). All reactions were carried out under nitrogen unless specified otherwise.

[00297] Example 13: tert-butyl 3-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate

[00298] 

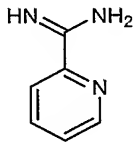
[00299] Synthesis was done according to a procedure published in J. Org. Chem. **43**, 3631-3632 (1978). To an ice-cold solution of 1-(tert-butoxycarbonyl)-3-piperidine carboxylic acid (10.0 g, 43.6 mmol), malononitrile (2.40 g, 36.35 mmol) and diethylcyanophosphonate (7.4 mL, 43.6 mmol) in THF (100 mL) was added triethylamine (16.2 mL, 116.3 mmol). The resulting solution was stirred at 0°C for 2 h, then at room temperature overnight. The reaction was quenched by adding an aqueous solution of 1 N HCl (50 mL) followed by a dilution with CH_2Cl_2 (100 mL). The aqueous phase was extracted with CH_2Cl_2 (1 x 100 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (2 x 50 mL). The later aqueous phase was back-extracted with CH_2Cl_2 (1 x 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to dryness under reduced pressure. The residue (~36 mmol) was dissolved in a mixture of 1,4-dioxane (109 mL) and water (9.0 mL). To this solution was added $NaHCO_3$ (12.2 g, 145.2 mmol) and dimethylsulfate (11.2 mL, 117.7 mmol). The resulting mixture was heated to reflux for 45 min. To the cooled reaction mixture was added water (198 mL). The solution thus obtained was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (eluents, 2:1 to 1:1 hexanes/EtOAc) gave the title compound as a yellow oil.

[00300] Example 14: tert-butyl 2-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate

[00301] 

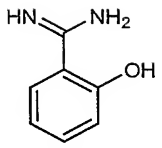
[00302] Prepared according to the procedure of **Example 13.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (br s, 1H), 4.36 (s, 3H), 3.81 (br s, 1H), 3.15 (br s, 1H), 1.98-1.84 (m, 2H), 1.68-1.54 (m, 4H), 1.47 (s, 9H).

[00303] Example 15: pyridine-2-carboximidamide

[00304] 

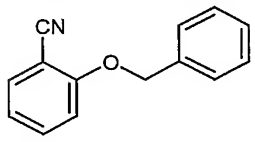
[00305] To a slurry of NH_4Cl (4.62 g, 86.4 mmol) in toluene (34 mL) at 0°C was added dropwise a solution of $Al(CH_3)_3$ (7.6 mL, 79.7 mmol) in toluene (32 mL). The reaction mixture was warmed to room temperature and stirred for 2 h prior to the addition of a solution of 2-cyanopyridine (5.0 g, 48.0 mmol) in toluene (15.0 mL). The resulting solution was heated to 80°C for 20 h. The cooled reaction mixture was poured into a slurry of silica gel (24.0 g) in $CHCl_3$ (80 mL), followed by vigorous stirring for 10 min. The silica gel was filtered off and the cake was rinsed in turn with methanol and an aqueous solution of 2N NaOH (100 mL). The combined filtrates were extracted with $CHCl_3$ (3 x 300 mL), then concentrated to dryness under reduced pressure, diluted with a small amount of methanol, and treated with a 2N HCl solution in methanol. The precipitate that formed was isolated by filtration and dried in a vacuum oven to afford the title compound as an off-white HCl salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.66 (s, 2H), 9.52 (s, 2H), 8.85-8.81 (m, 1H), 8.37 (d, J = 7.9 Hz, 1H), 8.17 (td, J = 1.8, 1.6 Hz, 1H), 7.80 (ddd, J = 7.7, 4.7, 0.9 Hz, 1H).

[00306] Example 16: 2-hydroxybenzenecarboximidamide



[00307]

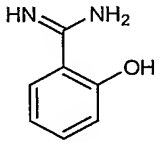
[00308] Step 1: Preparation of 2-benzyloxy-benzonitrile



[00309]

[00310] To a slurry of 2-cyanophenol (25.0 g, 209.9 mmol), K_2CO_3 (46.4 g, 335.8 mmol) in acetone (1.05 L) was added benzyl bromide (30.0 mL, 252.2 mmol) and NaI (2.0 g, 13.4 mmol). The reaction mixture was stirred for 24 h at room temperature, then filtered. The filtrate was concentrated to dryness under reduced pressure. Purification by flash column chromatography (eluent, hexanes to 95:5 hexanes/EtOAc to 95:0.5:0.5 to 8:1.5:0.5 CH_2Cl_2/hexanes/EtOAc) gave the desired product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, J = 7.8, 1.6 Hz, 1H), 7.51-7.43 (m, 3H), 7.41-7.35 (m, 2H), 7.34-7.30 (m, 1H), 7.00-6.96 (m, 2H), 5.20 (s, 2H).

[00311] Step 2: Preparation of 2-hydroxybenzenecarboximidamide

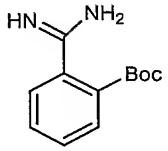


[00312]

[00313] To a slurry of NH_4Cl (20.2 g, 377.6 mmol) in toluene (147 mL) at 0°C was added dropwise a solution of $Al(CH_3)_3$ (33.4 mL, 348.6 mmol) in toluene (174 mL). The reaction mixture was warmed to room temperature and stirred for 2 h prior to the addition of a solution of 2-benzyloxy-benzonitrile (Step 1, 42.0 g, 210.0 mmol) in toluene (80.0 mL). The resulting solution was heated to 80°C for 20 h. The supernatant was discarded, and the solid residue at the bottom of the flask was suspended in a mixture of 2N aqueous solution of NaOH and MeOH, sonicated and filtered. That operation was repeated. The combined filtrates were extracted with $CHCl_3$, then with a mixture of

$CHCl_3$/isopropanol (80/20). The combined extracts were concentrated to dryness under reduced pressure. The final cake was suspended three times in a mixture of $CHCl_3$ and isopropanol (80/20), stirred overnight and then filtered. The combined filtrates were concentrated to dryness under reduced pressure. The residues were combined, dissolved in a minimum amount of MeOH, and treated with a 2N solution of HCl in MeOH. The precipitate that had formed was isolated by filtration and dried to afford the title compound as an off-white solid HCl salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.21 (s, 1H), 9.13 (s, 2H), 9.06 (s, 2H), 7.55 (dd, J = 7.8, 1.6 Hz, 1H), 7.49-7.43 (m, 1H), 7.16 (dd, J = 8.2, 0.7 Hz, 1H), 6.98-6.93 (m, 1H).

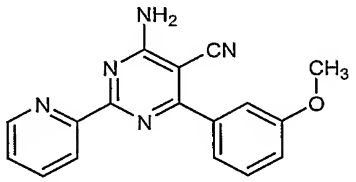
[00314] Example 17: tert-butyl 2-[amino(imino)methyl]benzoate

[00315] 

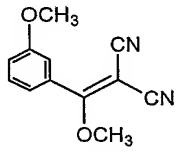
[00316] Into a solution of 2-benzyloxy-benzonitrile (**Example 4, Step 1**, 10.0 g, 47.8 mmol) in EtOH (200 mL) at -78°C was bubbled HCl gas for 2 h during which time the reaction mixture temperature rose to -50°C. The reaction mixture was warmed to 0°C and stirred overnight while warming to room temperature. The reaction mixture was diluted with EtOH (100.0 mL) and cooled to -78°C. Ammonia gas was then bubbled into the reaction solution for 1.5 h. The white slurry thus obtained was warmed to 0°C and ammonia bubbling was maintained overnight. The slurry was filtered and the cake was rinsed in turn with MeOH and EtOH. The filtrate was concentrated and the residue was diluted with CH_2Cl_2 (200 mL) and 2 N aqueous solution of NaOH (50 mL). The aqueous phase was extracted with CH_2Cl_2 (200 mL), $CHCl_3$ (200 mL) and with a 3/1 mixture of $CHCl_3$ and isopropanol (300 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give some unidentified impurities. The aqueous phase was concentrated to dryness

under reduced pressure to afford a white solid, which was triturated with a 6/1 mixture of CH_2Cl_2/MeOH and filtered. The cake was rinsed with the same solvent mixture. The filtrates were concentrated to dryness under reduced pressure to give a white solid, which was dissolved in MeOH and purified by flash column chromatography (eluent, 95/4.5/0.5 to 90/9/1 to 80/18/2 CH_2Cl_2/MeOH/conc'd NH_4OH) to give the title compound as an off-white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 7.52-7.45 (m, 3H), 7.42-7.30 (m, 4H), 7.16 (d, J = 7.9 Hz, 1H), 6.99 (dt, J = 7.4, 0.7 Hz, 1H), 5.15 (s, 2H).

[00317] Example 18: 4-amino-6-(3-methoxyphenyl)-2-pyridin-2-ylpyrimidine-5-carbonitrile

[00318] 

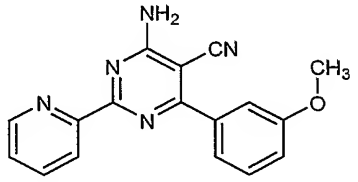
[00319] Step 1: Preparation of 2-(methoxy(3-methoxyphenyl)methylene)malononitrile

[00320] 

[00321] To a solution of malononitrile (1.94 g, 29.3 mmol) in THF (30 mL) at 0°C was added sodium hydride (60% in mineral oil, 2.34 g, 58.6 mmol); the reaction mixture was stirred for 30 min. 3-Methoxybenzoyl chloride (5.00 g, 29.3 mmol) was added at 0°C and the solution was slowly warmed to room temperature and stirred for 1 h. Dimethyl sulfate (7.39 g, 58.6 mmol) was then added and the reaction mixture was refluxed for 2 h. The reaction mixture was diluted with diethyl ether (40 mL) and washed with water (15 mL). The aqueous phase was then washed with diethyl ether (3 x 30 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. Purification by flash column

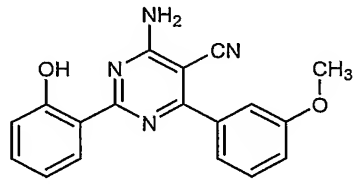
chromatography (eluent, 3:1 Hexanes/EtOAc; the mixture was loaded onto the column as a solution in CH_2Cl_2) gave the product as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (t, *J* = 8.0 Hz, 1H), 7.14 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.96 (s, 1H), 3.93 (s, 3H), 3.87 (s, 3H).

[00322] Step 2: Preparation of 4-amino-6-(3-methoxyphenyl)-2-pyridin-2-ylpyrimidine-5-carbonitrile

[00323]  (structure from ChemLink)

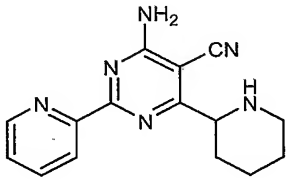
[00324] To a suspension of pyridine-2-carboximidamide (**Example 15**, 307 mg, 1.95 mmol) and the product obtained in Step 1 (500 mg, 2.33 mmol) in ethanol (20 mL) was added sodium methoxide (421 mg, 7.80 mmol) and stirred for 15 min at room temperature. The reaction mixture was then filtered and the remaining solid was washed with a solution of 9:1 ethanol/ water. Purification by preparative HPLC yielded the desired product, a portion of which was then dissolved in DMF and filtered. To the filtrate was added water and the title compound precipitated from solution as a white solid. mp 231-235°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.74 (d, *J* = 4.0 Hz, 1H), 8.55-7.65 (br s, 2H), 8.40 (d, *J* = 8.0 Hz, 1H), 7.98 (dt, *J* = 3.9, 1.8 Hz, 1H), 7.57-7.49 (m, 4H), 7.20-7.18 (m, 1H), 3.85 (s, 3H). ESI MS *m/z* 304 $[M+H]^+$. Anal. Calcd for $C_{17}H_{13}N_5O$: C, 67.32; H, 4.32; N, 23.09. Found: C, 67.24; H, 4.12; N, 22.82.

[00325] Example 19: 4-amino-2-(2-hydroxyphenyl)-6-(3-methoxyphenyl)pyrimidine-5-carbonitrile

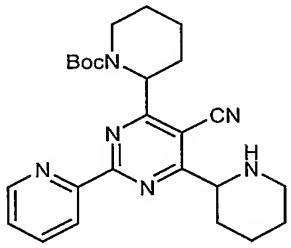
[00326] 

[00327] Prepared as a yellow solid following a procedure similar to that described in **Example 18, Step 2**, using 2-hydroxybenzenecarboximidamide (**Example 16**, 256 mg, 1.95 mmol) and the material obtained in **Example 18, Step 1** (500 mg, 2.33 mmol). mp 240-244°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.22 (s, 1H), 8.63 (br s, 1H), 8.37 (dd, J = 8.0, 2.0 Hz, 1H), 8.01 (br s, 1H), 7.55-7.44 (m, 4H), 7.23-7.20 (m, 1H), 6.97-6.93 (m, 2H), 3.86 (s, 3H). ESI MS *m/z* 319 $[M+H]^+$. Anal. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.92; H, 4.43; N, 17.60. Found: C, 67.56; H, 4.27; N, 17.25.

[00328] Example 20: 4-amino-6-piperidin-2-yl-2-pyridin-2-ylpyrimidine-5-carbonitrile

[00329] 

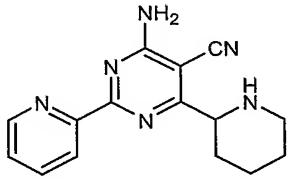
[00330] Step 1: Preparation of tert-butyl 2-(5-cyano-6-piperidin-2-yl-2-pyridin-2-ylpyrimidin-4-yl)piperidine-1-carboxylate

[00331] 

[00332] To a solution of pyridine-2-carboximidamide (**Example 15**, 300 mg, 1.90 mmol) and tert-butyl 2-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate (**Example 14**, 664 mg, 2.28 mmol) in ethanol (28 mL) was added sodium methoxide (411 mg, 7.60 mmol) and stirred at reflux for 3 h. The reaction mixture was then concentrated, filtered through silica gel eluting with 80:19:1 CH_2Cl_2/MeOH/concd NH_4OH. The filtrate was concentrated, diluted with water (15 mL) and extracted with CH_2Cl_2 (4 x 40 mL). The combined

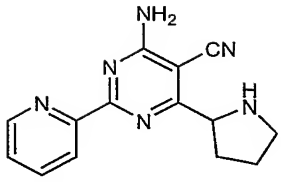
organic phase was dried (Na_2SO_4) and concentrated. Purification by flash column chromatography (eluent, 95:4.5:0.5 CH_2Cl_2/MeOH/concd NH_4OH; the mixture was loaded onto the column as a solution in CH_2Cl_2) gave the product as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.73 (d, J = 3.5 Hz, 1H), 8.10 (br s, 2H), 8.28 (d, J = 8.0 Hz, 1H), 7.99 (dt, J = 7.6, 1.5 Hz, 1H), 7.55-7.53 (m, 1H), 5.20 (s, 1H), 3.90 (dd, J = 10.5, 2.5 Hz, 1H), 3.62 (dt, J = 12.5, 3.0 Hz, 1H), 2.05 (br s, 1H), 1.95 (br s, 1H), 1.75 (br s, 1H), 1.57-1.53 (m, 1H), 1.50-1.38 (m, 2H), 1.25 (s, 9H).

[00333] Step 2: Preparation of 4-amino-6-piperidin-2-yl-2-pyridin-2-ylpyrimidine-5-carbonitrile

[00334] 

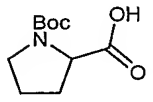
[00335] The product obtained in Step 1 (300 mg, 0.78 mmol) was dissolved in 4 N HCl (dioxane, 4 mL) and stirred for 15 min at room temperature, during which the desired product precipitated from solution. The reaction mixture was diluted with MeOH (2 mL), filtered and washed with ether to give the title compound as a white solid. mp 235-250°C dec. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.74-9.71 (m, 1H), 9.49 (br s, 1H), 8.94 (d, J = 4.8 Hz, 1H), 8.83 (br s, 1H), 8.70 (d, J = 7.8 Hz, 1H), 8.49-8.37 (m, 2H), 7.99 (s, 1H), 4.60 (t, J = 9.6 Hz, 1H), 3.44-3.37 (m, 1H), 3.22-3.19 (m, 1H), 2.14 (d, J = 9.6 Hz, 1H), 1.89-1.68 (m, 5H). ESI MS m/z 280 $[M+H]^+$. Anal. Calcd for $C_{15}H_{16}N_6 \cdot 2HCl \cdot H_2O$: C, 48.53; H, 5.43; N, 22.64. Found: C, 48.58; H, 5.25; N, 22.39.

[00336] Example 21: 4-amino-2-pyridin-2-yl-6-pyrrolidin-2-ylpyrimidine-5-carbonitrile



[00337]

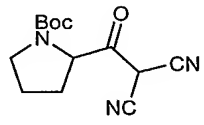
[00338] Step 1: Preparation of 1-(tert-butoxycarbonyl)proline



[00339]

[00340] To a suspension of proline (10.0 g, 86.9 mmol) in DMF (200 mL) was added di-*tert*-butyl dicarbonate (37.98 g, 174 mmol) followed by triethylamine (17.6 g, 174 mmol). The reaction mixture was stirred overnight at room temperature. The solution was diluted with water (200 mL) and extracted first with EtOAc (2 x 400 mL) followed by CH_2Cl_2 (3 x 400 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. The crude product was carried forth to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37-4.22 (m, 1H), 3.57-3.39 (m, 2H), 2.70-1.89 (m, 4H), 1.48-1.40 (m, 9H).

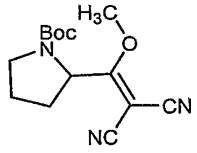
[00341] Step 2: Preparation of tert-butyl 2-(dicyanoacetyl)pyrrolidine-1-carboxylate



[00342]

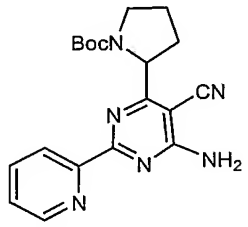
[00343] To a solution of the product obtained in Step 1 (~43 mmol) in THF (100 mL) at room temperature was added malononitrile (2.39 g, 36.2 mmol) and diethylcyanophosphonate (7.60 g, 43.5 mmol). The reaction solution was then cooled to 0°C prior to the addition of triethylamine (11.7 g, 116 mmol). The solution was stirred for 2 h at 0°C and at room temperature overnight. The reaction mixture was diluted with an aqueous solution of 1 N HCl (33 mL) and extracted with CH_2Cl_2 (4 x 60 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70-4.66 (m, 1H), 3.47-3.41 (m, 2H), 2.31-2.24 (m, 1H), 1.91-1.81 (m, 4H), 1.43 (s, 9H).

[00344] Step 3: Preparation of tert-butyl 2-(2,2-dicyano-1-methoxyvinyl)pyrrolidine-1-carboxylate

[00345] 

[00346] To a mixture of the product obtained in Step 2 (~43 mmol) in 1,4-dioxane (120 mL) and water (10 mL) was added sodium bicarbonate (14.62 g, 174 mmol) and dimethyl sulfate (19.20 g, 152 mmol). The reaction mixture was then refluxed for 2 h, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. Purification by flash column chromatography (eluent, 2:1 Hexanes/EtOAc; the mixture was loaded onto the column as a solution in CH_2Cl_2) gave the product (4.84 g, 40% over three steps) as a 1:1 mixture of rotamers in the form of an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (dd, J = 8.4, 5.5 Hz, 1H), 4.72 (dd, J = 8.3, 5.8 Hz, 1H), 4.34 (s, 3H), 4.29 (s, 3H), 3.61-3.56 (m, 1H), 3.50-3.42 (m, 3H), 2.49-2.44 (m, 2H), 1.99-1.89 (m, 6H), 1.48 (s, 9H), 1.47 (s, 9H).

[00347] Step 4: Preparation of tert-butyl 2-(6-amino-5-cyano-2-pyridin-2-ylpyrimidin-4-yl)pyrrolidine-1-carboxylate

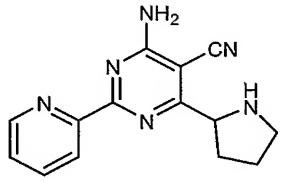
[00348] 

[00349] The above compound was prepared in 62% yield as a tan solid following a procedure similar to that described in **Example 18, Step 2**, using pyridine-2-carboximidamide (**Example 15**, 300 mg, 1.90 mmol) and the material obtained in Step 3 (633 mg, 2.28 mmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.72 (d, J = 4.5 Hz, 1H), 8.39-7.68 (br s, 2H), 8.30-8.28 (m, 1H), 7.97 (dt, J = 7.8, 1.7 Hz, 1H), 7.54-7.52 (m, 1H), 4.87-4.84 (m, 1H), 3.60-3.55 (m, 1H),

3.53-3.49 (m, 1H), 2.41-2.38 (m, 1H), 2.06-2.00 (m, 1H), 1.94-1.86 (m, 2H), 1.37 (s, 3H), 1.12 (s, 6H).

[00350] Step 5: Preparation of 4-amino-2-pyridin-2-yl-6-pyrrolidin-2-ylpyrimidine-5-carbonitrile

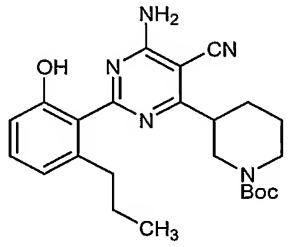
[00351]



[00352] Prepared as a white solid following a procedure similar to that described in **Example 20, Step 2**, using the material obtained in Step 4 (300 mg, 0.823 mmol). mp 240-245°C dec. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.39 (br s, 1H), 9.52 (br s, 1H), 8.97 (s, 1H), 8.45 (br s, 1H), 8.69 (d, J = 7.5, 1H), 8.58 (s, 1H), 8.41 (br s, 1H), 8.07 (s, 1H), 4.96 (q, J = 7.1 Hz, 1H), 3.62-3.57 (m, 1H), 3.40 (m, 1H), 2.58-2.54 (m, 1H), 2.09-1.96 (m, 3H). ESI MS *m/z* 267 $[M+H]^+$. Anal. Calcd for $C_{14}H_{14}N_6 \cdot 2HCl \cdot 0.25H_2O$: C, 48.92; H, 4.84; N, 24.45. Found: C, 49.23; H, 4.65; N, 24.15.

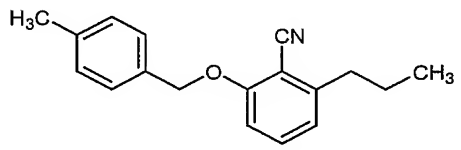
[00353] Example 22: tert-butyl 3-[6-amino-5-cyano-2-(2-hydroxy-6-propylphenyl)pyrimidin-4-yl]piperidine-1-carboxylate

[00354]



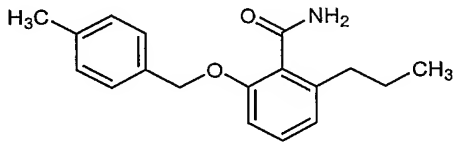
[00355] Step 1: Preparation of 2-[(4-methylbenzyl)oxy]-6-propylbenzonitrile

[00356]



[00357] To a suspension of 2-fluoro-6-[(4-methylbenzyl)oxy]benzonitrile (5.0 g, 20.7 mmol) and $MnCl_2$ (2.60 g, 20.7 mmol) in THF (50 mL) was added n-PrMgCl (2.0 M in ether, 31 mL, 62 mmol) slowly at 0°C. The solid gradually dissolved to give a brown solution. The reaction was allowed to warm up to room temperature and was stirred for 3 h, then slowly poured into an ice-cooled NH_4Cl solution (200 mL). The product was extracted with ethyl acetate (3 x 150 mL). The combined organic phase was washed with brine (150 mL), dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by flash column chromatography (1:19 to 1:1 ethyl acetate/hexanes) to provide the desired product as a viscous oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.33 (m, 3H), 7.20 (d, *J* = 7.8 Hz, 2H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.15 (s, 2H), 2.78 (t, *J* = 7.5 Hz, 2H), 2.35 (s, 3H), 1.74-1.66 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

[00358] Step 2: Preparation of 2-[(4-methylbenzyl)oxy]-6-propylbenzonitrile

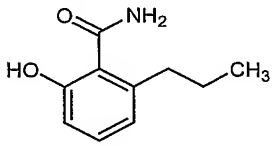


[00359]

[00360] To a solution of 2-[(4-methylbenzyl)oxy]-6-propylbenzonitrile (Step 1, 1.0 g, 3.8 mmol) in benzyl alcohol (2.6 mL) was added KOH (0.52 g, 9.4 mmol) and H_2O (0.35 mL, 19.4 mmol). The reaction mixture and heated to 120°C for 3 h. The cooled reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (200 mL). The aqueous layer was extracted with ethyl acetate (100 mL). The combined organic extracts were washed with brine (150 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:19 to 1:0 ethyl acetate/hexanes) to provide the desired compound as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.20 (m, 3H), 7.18 (d, *J* = 7.8 Hz, 2H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 5.78 (s, 2H), 5.05 (s, 2H), 2.68 (t, *J* = 7.7

Hz, 2H), 2.34 (s, 3H), 1.69-1.59 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). ESI MS *m/z* 284 $[M+H]^+$.

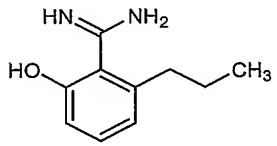
[00361] Step 3: Preparation of 2-hydroxy-6-propylbenzamide



[00362]

[00363] To a solution of the material obtained in Step 2 (1.0 g, 3.5 mmol), in a mixture of ethanol/ethyl acetate (40 mL/20 mL) was added Pd/C (0.5 g). The reaction mixture was agitated on a Parr hydrogenator at 40 psi for 14 h at room temperature. The mixture was filtered through a short pad of diatomaceous earth. The filtrate was concentrated to give the product as a white solid. ^{1}H NMR (500 MHz, acetone-d_6): δ 9.4 (s, 1H), 7.14 (t, J = 7.8 Hz, 1H), 6.99 (br s, 2H), 6.74-6.71 (m, 2H), 2.68 (t, J = 7.1 Hz, 2H), 1.66-1.59 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H). ESI MS *m/z* 180 $[M+H]^+$.

[00364] Step 4: Preparation of 2-hydroxy-6-propylbenzamidine



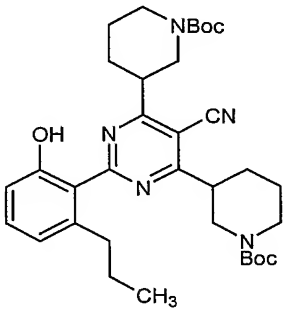
[00365]

[00366] To a suspension of the material obtained in Step 3 (0.59 g 3.3 mmol) in $CHCl_3$ (15 mL) was added trimethyloxonium tetrafluoroborate (0.59 g, 3.95 mmol) at room temperature. The mixture was stirred at room temperature for 14 h. The solvent was removed and the residue was transferred into a sealed tube with methanol (2 mL). Ammonia (7.0 N in MeOH, 8 mL) was added and the reaction mixture was heated to 80°C for 14 h. The reaction mixture was then concentrated to a smaller volume under reduced pressure. The residue was diluted with ethyl acetate (100 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (100 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic extracts were washed with brine (150 mL), dried (Na_2SO_4) and concentrated under vacuum. The residue was

purified by flash column chromatography (eluent, 90:9:1 CH_2Cl_2/MeOH/concd NH_4OH to 9:1 MeOH/concd NH_4OH) to provide the product as a white solid. ^1H NMR (300 MHz, CD_3OD-d_4): δ 7.26 (t, J = 7.9 Hz, 1H), 6.82-6.76 (m, 2H), 2.63 (t, J = 7.7 Hz, 2H), 1.76-1.63 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H). ESI MS *m/z* 179 $[M+H]^+$.

[00367] Step 5: Preparation of tert-butyl 3-[6-amino-5-cyano-2-(2-hydroxy-6-propylphenyl)pyrimidin-4-yl]piperidine-1-carboxylate

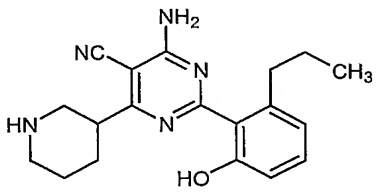
[00368]



[00369] To a suspension of the material from Step 4 (127 mg, 0.71 mmol) and tert-butyl 3-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate (**Example 13**, 250 mg, 0.86 mmol) in anhydrous ethanol was added sodium methoxide powder (154 mg, 2.85 mmol) at room temperature. The reaction mixture was then refluxed for 1 h. The reaction was cooled to room temperature and poured into a saturated aqueous solution of NH_4Cl (100 mL). The product was extracted with ethyl acetate (2 x 100 mL). The organics were combined, washed with brine, dried (Na_2SO_4) and concentrated under vacuum. The material was purified by flash column chromatography (eluent, 90:9:1 CH_2Cl_2/MeOH/concd NH_4OH). A second purification by Biotage HPFC (17:83 to 28:72 ethyl acetate/hexanes) gave the title compound as a yellow solid. mp 192-193°C. ^1H NMR (300 MHz, $CDCl_3$) δ 12.70 (s, 1H), 7.26 (t, J = 6.3 Hz, 1H), 6.86-6.78 (m, 2H), 5.67 (s, 2H), 3.14-3.03 (m, 4H), 2.15-1.56 (m, 8H), 1.48 (s, 9H), 0.95 (t, J = 7.2 Hz, 3H). ESI MS *m/z* 438 $[M+H]^+$. Anal. Calcd for $C_{24}H_{31}N_5O_2$: C, 65.88; H, 7.14; N, 16.01. Found: C, 65.94; H, 7.24; N, 15.79.

[00370] Example 23: 4-amino-2-(2-hydroxy-6-propylphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile

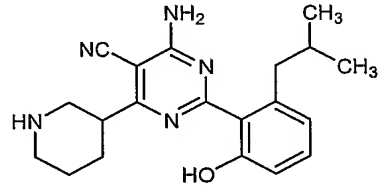
[00371]



[00372] To tert-butyl 3-[6-amino-5-cyano-2-(2-hydroxy-6-propylphenyl)pyrimidin-4-yl]piperidine-1-carboxylate (**Example 22**, 0.50 g, 1.1 mmol) in a round bottom flask was added a solution of 4N HCl in 1,4-dioxane (5 mL) at room temperature. The reaction mixture was stirred for 1.5 h at room temperature. The solvent was removed at room temperature under vacuum. Trituration with a mixture of methanol/ether provided the title compound as a light yellow solid. mp 150°C dec. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.17-8.90 (m, 2H), 7.94 (br s, 2H), 7.13 (t, J = 7.8 Hz, 1H), 6.76-6.69 (m, 2H), 3.65-3.14 (m, 4H), 3.00-2.80 (m, 1H), 2.53-2.49 (m, 2H), 2.05-1.50 (m, 4H), 1.43-1.36 (m, 2H), 0.78 (t, J = 7.3 Hz, 3H). ESI MS *m/z* 338 $[M+H]^+$. Anal. Calcd for $C_{19}H_{23}N_5O \cdot HCl \cdot H_2O$: C, 58.23; H, 6.69; N, 17.87. Found: C, 58.37; H, 6.52; N, 17.56.

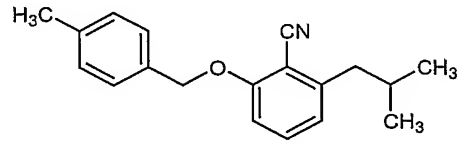
[00373] Example 24: 4-amino-2-(2-hydroxy-6-isobutylphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile

[00374]



[00375] Step 1: Preparation of 2-isobutyl-6-[(4-methylbenzyl)oxy]benzonitrile

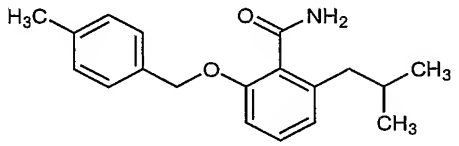
[00376]



[00377] Prepared as a colorless oil following a procedure similar to that described in **Example 22, Step 1**, using 2-fluoro-6-[(4-methylbenzyl)oxy]benzonitrile (5.0 g, 18.9 mmol) and isobutyl magnesium chloride (3.8 g, 13.6 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.31 (m, 3H), 7.20 (d, *J* = 7.9 Hz, 2H), 6.83-6.80 (m, 2H), 5.18 (s, 2H), 2.68 (d, *J* = 7.3 Hz, 2H), 2.35 (s, 3H), 2.02-1.95 (m, 1H), 0.95 (d, *J* = 7.2 Hz, 6H).

[00378] Step 2: Preparation of 2-isobutyl-6-[(4-methylbenzyl)oxy]benzamide

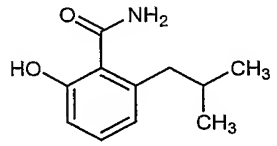
[00379]



[00380] Prepared as a white solid following a procedure similar to that described in **Example 22, Step 2**, starting with 2-isobutyl-6-[(4-methylbenzyl)oxy]benzonitrile (Step 1, 3.8 g, 13.6 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, *J* = 7.9 Hz, 2H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 2H), 6.83-6.81 (m, 2H), 5.74 (s, 2H), 5.05 (s, 2H), 2.61 (d, *J* = 7.3 Hz, 2H), 2.35 (s, 3H), 2.01-1.90 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 6H). ESI MS *m/z* 298 $[M+H]^+$.

[00381] Step 3: Preparation of 2-hydroxy-6-isobutylbenzamide

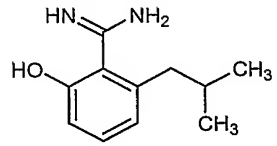
[00382]



[00383] Prepared as a white solid following a procedure similar to that described in **Example 22, Step 3**, starting with 2-isobutyl-6-[(4-methylbenzyl)oxy]benzamide (Step 2, 0.76 g, 2.6 mmol). ESI MS *m/z* 194 $[M+H]^+$.

[00384] Step 4: Preparation of 2-hydroxy-6-isobutylbenzamidine

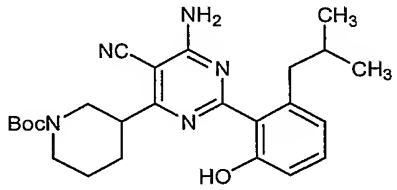
[00385]



[00386] Prepared as a white solid following a procedure similar to that described in **Example 22, Step 4**, starting with 2-hydroxy-6-isobutylbenzamide (Step 3, 0.50 g, 26 mmol). ^{1}H NMR (300 MHz, CD_3OD-d_4): δ 7.26 (t, J = 7.9 Hz, 1H), 6.81-6.75 (m, 2H), 2.54 (d, J = 7.3 Hz, 2H), 2.03-1.91 (m, 1H), 0.95 (d, J = 6.5 Hz, 6H). ESI MS *m/z* 193 $[M+H]^+$.

[00387] Step 5: Preparation of tert-butyl 3-[6-amino-5-cyano-2-(2-hydroxy-6-isobutylphenyl)pyrimidin-4-yl]piperidine-1-carboxylate

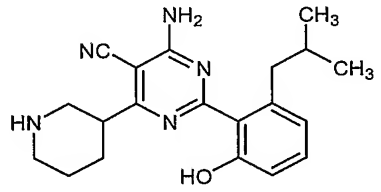
[00388]



[00389] Prepared as a light yellow solid following a procedure similar to that described in **Example 22, Step 5**, starting with 2-hydroxy-6-isobutylbenzamidine (Step 4, 0.20, 1.06 mmol) and tert-butyl 3-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate (**Example 13**, 0.43 g, 1.5 mmol). ESI MS *m/z* 452 $[M+H]^+$.

[00390] Step 6: Preparation of 4-amino-2-(2-hydroxy-6-isobutylphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile

[00391]

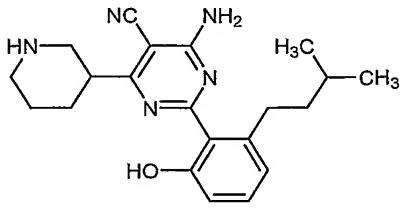


[00392] Prepared as a light yellow solid following a procedure similar to **Example 23**, starting with tert-butyl 3-[6-amino-5-cyano-2-(2-hydroxy-6-isobutylphenyl)pyrimidin-4-yl]piperidine-1-carboxylate (Step 5, 0.23 g, 0.50 mmol). ^{1}H NMR (300 MHz, CD_3OD-d_4): δ 9.08-8.80 (m, 2H), 8.0 (br s, 2H), 7.14 (t, J = 7.8 Hz, 1H), 6.76 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.4 Hz, 1H), 3.40-3.15 (m, 4H), 3.12-2.89 (m, 1H), 2.46-2.42 (m, 2H), 2.05-1.50 (m, 5H), 0.72 (d, J =

6.5 Hz, 6H). ESI MS *m/z* 352 $[M+H]^+$. Anal. Calcd for $C_{20}H_{25}N_5O \cdot 2HCl \cdot H_2O$: C, 54.30; H, 6.61; N, 15.83. Found: C, 54.61; H, 6.45; N, 15.68.

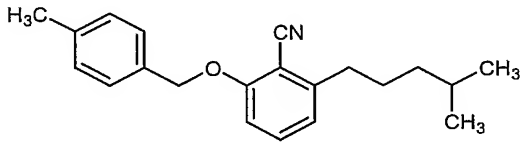
[00393] Example 25: 4-amino-2-[2-hydroxy-6-(3-methylbutyl)phenyl]-6-piperidin-3-ylpyrimidine-5-carbonitrile

[00394]



[00395] Step 1: Preparation of 2-[(4-methylbenzyl)oxy]-6-(4-methylpentyl)benzonitrile

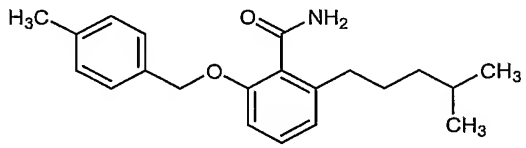
[00396]



[00397] Prepared as a colorless oil following a procedure similar to that described in **Example 22, Step 1**, using 2-fluoro-6-[(4-methylbenzyl)oxy]benzonitrile (5.0 g, 20.7 mmol) and 3-methylbutyl magnesium bromide (2.0 M in ether, 31 mL, 62 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.33 (m, 3H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.05 (s, 2H), 2.81-2.78 (m, 2H), 2.35 (s, 3H), 1.66-1.60 (m, 1H), 1.56-1.51 (m, 2H), 0.96 (d, *J* = 6.6 Hz, 6H).

[00398] Step 2: Preparation of 2-[(4-methylbenzyl)oxy]-6-(4-methylpentyl)benzamide

[00399]

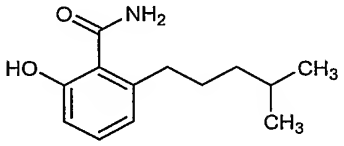


[00400] Prepared as a white solid following a procedure similar to that described in **Example 22, Step 2**, starting with 2-[(4-methylbenzyl)oxy]-6-(4-methylpentyl)benzonitrile (Step 1, 4.8 g, 16.4 mmol). ^{1}H NMR (500 MHz,

acetone-d_6): δ 7.38 (d, J = 7.9 Hz, 2H), 7.21-7.16 (m, 3H), 6.96-6.88 (m, 2H), 6.84-6.82 (d, J = 7.6 Hz, 1H), 6.66 (br s, 1H), 5.06 (s, 2H), 2.77-2.64 (m, 2H), 2.31 (s, 3H), 1.59-1.51 (m, 3H), 0.92 (d, J = 6.5 Hz, 6H). ESI MS m/z 312 $[M+H]^+$.

[00401] Step 3: Preparation of 2-hydroxy-6-(4-methylpentyl)benzamide

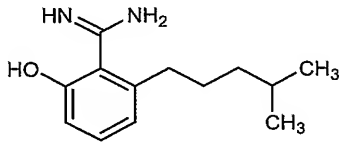
[00402]



[00403] Prepared as a white solid following a procedure similar to that described in **Example 22, Step 3**, starting with 2-[(4-methylbenzyl)oxy]-6-(4-methylpentyl)benzamide (Step 2, 2.8 g, 9.0 mmol). ^{1}H NMR (500 MHz, acetone-d_6): δ 9.41 (s, 1H), 7.18-7.10 (m, 1H), 7.02 (br s, 2H), 6.74-6.70 (m, 2H), 2.84-2.78 (m, 2H), 1.58-1.48 (m, 3H), 0.92 (d, J = 6.5 Hz, 6H). ESI MS m/z 208 $[M+H]^+$.

[00404] Step 4: Preparation of 2-hydroxy-6-(4-methylpentyl)benzenecarboximidamide

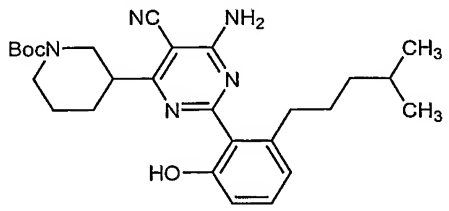
[00405]



[00406] Prepared as a white solid following a procedure similar to that described in **Example 22, Step 4**, starting with 2-hydroxy-6-(4-methylpentyl)benzamide (Step 3, 1.8 g, 9.2 mmol). ESI MS m/z 207 $[M+H]^+$.

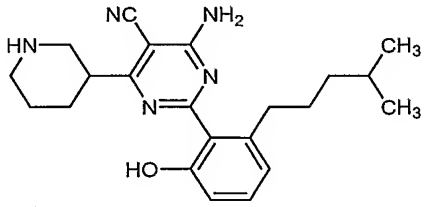
[00407] Step 5: Preparation of tert-butyl 3-{6-amino-5-cyano-2-[2-hydroxy-6-(4-methylpentyl)phenyl]pyrimidin-4-yl}piperidine-1-carboxylate

[00408]



[00409] Prepared as a light yellow solid following a procedure similar to that described in **Example 22, Step 5**, starting with 2-hydroxy-6-(4-methylpentyl)benzenecarboximidamide (Step 4, 0.48 g, 2.3 mmol) and tert-butyl 3-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate (**Example 13**, 1.36 g, 4.7 mmol). ESI MS *m/z* 466 $[M+H]^+$.

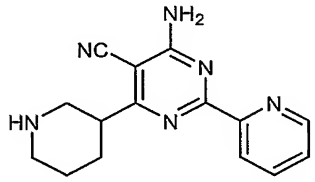
[00410] Step 6: Preparation of 4-amino-2-[2-hydroxy-6-(3-methylbutyl)phenyl]-6-piperidin-3-ylpyrimidine-5-carbonitrile



[00411]

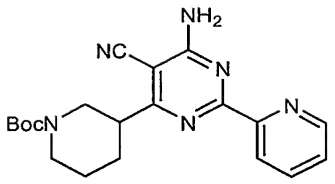
[00412] Prepared as a light yellow solid following a procedure similar to **Example 23**, starting with tert-butyl 3-{6-amino-5-cyano-2-[2-hydroxy-6-(4-methylpentyl)phenyl]pyrimidin-4-yl}piperidine-1-carboxylate (Step 5, 0.38 g, 0.82 mmol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.08-8.80 (m, 2H), 8.0 (br s, 2H), 7.13 (t, J = 7.8 Hz, 1H), 6.76 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 7.4 Hz, 1H), 3.40-3.15 (m, 4H), 3.12-2.89 (m, 1H), 2.46-2.42 (m, 2H), 2.05-1.50 (m, 5H), 0.72 (d, J = 6.5 Hz, 6H). ESI MS *m/z* 366 $[M+H]^+$. Anal. Calcd for $C_{21}H_{25}N_5O \cdot HCl \cdot 0.75H_2O$: C, 60.71; H, 7.16; N, 16.86. Found: C, 60.91; H, 6.91; N, 16.80.

[00413] Example 26: 4-amino-6-piperidin-3-yl-2-pyridin-2-ylpyrimidine-5-carbonitrile



[00414]

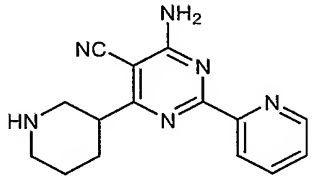
[00415] Step 1: Preparation of tert-butyl 3-(6-amino-5-cyano-2-pyridin-2-ylpyrimidin-4-yl)piperidine-1-carboxylate



[00416]

[00417] Prepared as a light yellow solid following a procedure similar to that described in **Example 22, Step 5**, starting with pyridine-2-carboximidamide (**Example 15**, 0.5 g, 3.2 mmol) and tert-butyl 3-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate (**Example 13**, 1.0 g, 3.4 mmol). ESI MS *m/z* 381 $[M+H]^+$

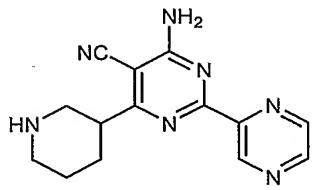
[00418] Step 2: Preparation of 4-amino-6-piperidin-3-yl-2-pyridin-2-ylpyrimidine-5-carbonitrile



[00419]

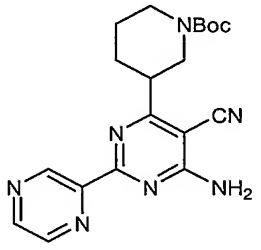
[00420] Prepared as a white solid (0.54 g, 1.92 mmol) following a procedure similar to **Example 23**, starting with tert-butyl 3-(6-amino-5-cyano-2-pyridin-2-ylpyrimidin-4-yl)piperidine-1-carboxylate (Step 1, 0.80 g, 2.1 mmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.42-9.40 (m, 1H), 9.01-8.99 (m, 1H), 8.89-8.88 (m, 1H), 8.51-8.50 (m, 1H), 8.46-6.44 (m, 1H), 7.88-7.87 (m, 1H), 3.59-3.28 (m, 4H), 3.04-2.98 (m, 1H), 1.98-1.84 (m, 4H). ESI MS *m/z* 281 $[M+H]^+$. Anal. Calcd for $C_{15}H_{16}N_6 \cdot 2HCl \cdot 2H_2O$: C, 46.28; H, 5.70; N, 21.59. Found: C, 46.25; H, 5.35; N, 21.61.

[00421] Example 27: 4-amino-6-piperidin-3-yl-2-pyrazin-2-ylpyrimidine-5-carbonitrile



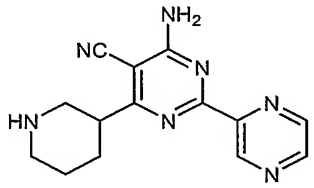
[00422]

[00423] Step 1: Preparation of tert-butyl 3-(6-amino-5-cyano-2-pyrazin-2-ylpyrimidin-4-yl)piperidine-1-carboxylate

[00424] 

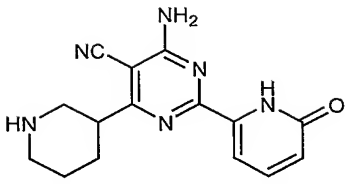
[00425] Prepared as a light yellow solid following a procedure similar to that described in **Example 22, Step 5**, starting with commercially available pyrazine-2-carboxamidine (0.13 g, 0.82 mmol) and tert-butyl 3-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate (**Example 13**, 0.20 g, 0.69 mmol). ESI MS *m/z* 382 $[M+H]^+$.

[00426] Step 2: Preparation of 4-amino-6-piperidin-3-yl-2-pyrazin-2-ylpyrimidine-5-carbonitrile

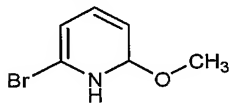
[00427] 

[00428] Prepared as a light yellow solid following a procedure similar to **Example 23**, starting with tert-butyl 3-(6-amino-5-cyano-2-pyrazin-2-ylpyrimidin-4-yl)piperidine-1-carboxylate (Step 1, 0.2 g, 0.52 mmol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.54 (m, 1H), 9.23-9.20 (m, 1H), 8.93-8.81 (m, 3H), 8.70-7.70 (m, 2H), 3.41-3.23 (m, 4H), 3.01-2.97(m, 1H), 2.05-1.75 (m, 4H). ESI MS *m/z* 282 $[M+H]^+$. Anal. Calcd for $C_{15}H_{16}N_6 \cdot HCl \cdot 0.25H_2O$: C, 52.18; H, 5.16; N, 30.42. Found: C, 52.16; H, 4.99; N, 30.18.

[00429] Example 28: 4-amino-2-(6-oxo-1,6-dihydropyridin-2-yl)-6-piperidin-3-ylpyrimidine-5-carbonitrile

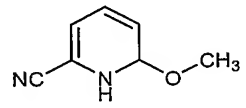
[00430] 

[00431] Step 1: Preparation of 6-bromo-2-methoxy-1,2-dihydropyridine

[00432] 

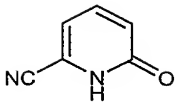
[00433] To a solution of 2,6-dibromopyridine (5.0 g, 21.1 mmol) in MeOH was added NaOMe (30% in MeOH, 4 mL, 21.1 mmol). The solution was refluxed for 14 h, then concentrated to dryness under reduced pressure. The residue was diluted with ethyl acetate (200 mL) and washed with H_2O (200 mL) and brine (200 mL). The extracts were dried (Na_2SO_4) and concentrated to provide a colorless oil. ESI MS *m/z* 188 $[M+H]^+$. The crude product was used as is in the next reaction without purification.

[00434] Step 2: Preparation of 1,6-dihydro-6-methoxypyridine-2-carbonitrile

[00435] 

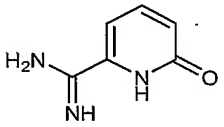
[00436] To a solution of 6-bromo-2-methoxy-1,2-dihydropyridine (Step 1, 4.0 g, 21.2 mmol) in DMF (40 mL) was added CuCN (2.3 g, 25.4 mmol) at room temperature. The reaction mixture was heated to 150°C overnight. The reaction was poured into a solution of ethylenediamine in H_2O (10%, 220 mL). The mixture was vigorously shaken. Ethyl acetate (2 x 100 mL) was used to extract the product. The organic extracts were combined, washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash column chromatography (eluent, 1:5 ethyl/hexanes) provided the product as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68-7.63 (m, 1H), 7.31-7.26 (m, 1H), 6.98-6.95 (m, 1H), 3.96 (s, 3H). ESI MS *m/z* 135 $[M+H]^+$.

[00437] Step 3: Preparation of 1,6-dihydro-6-oxopyridine-2-carbonitrile

[00438] 

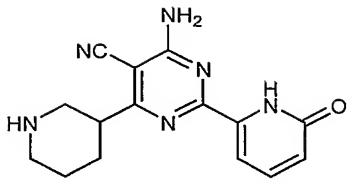
[00439] To a solution of 1,6-dihydro-6-methoxypyridine-2-carbonitrile (Step 2, 1.0 g, 7.46 mmol) in acetonitrile (27 mL) cooled to 0°C was added NaI (1.79 g, 11.9 mmol), TMSCl (1.53 mL, 11.9 mmol) and H_2O (53 µL, 2.93 mmol). The mixture was then heated at 65°C for 60 h. The cooled reaction mixture was poured into 10% $NaHSO_3$ solution (100 mL). The product was extracted with ethyl acetate (2 x 100 mL). The organic extracts were combined, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (19:1 CH_2Cl_2/MeOH) to provide a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.81 (s, 1H), 7.84-7.78 (m, 1H), 7.45 (d, J = 7.0 Hz, 1H), 6.97 (d, J = 8.6 Hz, 1H). ESI MS *m/z* 121 $[M+H]^+$.

[00440] Step 4: Preparation of 1,6-dihydro-6-oxopyridine-2-carboxamidine

[00441] 

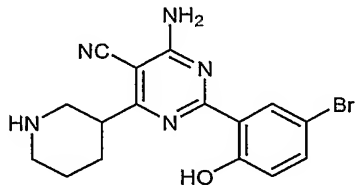
[00442] To 1,6-dihydro-6-oxopyridine-2-carbonitrile (Step 3, 0.9 g, 6.71 mmol) cooled to 0°C was added $LiN(TMS)_2$ in THF (1.0M, 8.05 mL) in one portion. The reaction was allowed to warm up to room temperature and was stirred for 14 h. The reaction mixture was added to a solution of 2.0N HCl in ether slowly to give a white viscous precipitate. Ether was evaporated and the residual aqueous solution was basified to pH 11 using 2.0N NaOH. The product was extracted with ethyl acetate (3 x 100 mL). The organic extracts were combined, washed with brine, dried (Na_2SO_4) and concentrated to provide the product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56-7.48 (m, 2H), 6.70-6.65 (m, 2H), 3.78 (s, 3H). ESI MS *m/z* 152 $[M+H]^+$.

[00443] Step 5: Preparation of 4-amino-2-(6-oxo-1,6-dihydropyridin-2-yl)-6-piperidin-3-ylpyrimidine-5-carbonitrile

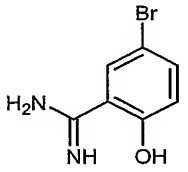
[00444] 

[00445] To a solution of 1,6-dihydro-6-oxopyridine-2-carboxamidine (Step 4, 0.33 g, 2.4 mmol) in DMF (4 mL) was added NaH (60% in mineral oil, 0.23 g, 9.6 mmol), and the reaction mixture was stirred for 10 min at room temperature. To the resulting mixture was added tert-butyl 3-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate (**Example 13**, 0.25 g, 0.86 mmol) in DMF (2 mL) and the resulting mixture was stirred for 1 h at room temperature. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl (100 mL) and the product was extracted with ethyl acetate (2 x 100 mL). The organic extracts were combined, washed with brine (100 mL), dried (Na_2SO_4) and concentrated. The material was purified by Biotage HPFC (98.5:1.5 to 95:5 CH_2Cl_2/MeOH) to provide the product as a yellow solid: ESI MS *m/z* 397 $[M+H]^+$. To the yellow solid in a round bottom flask was added 4N HCl in 1,4-dioxane (5 mL). The mixture was stirred for 45 min at room temperature. The solvent was removed under vacuum and the residue was triturated with MeOH/ether to provide the title compound as a light yellow solid. ^1H NMR (300 MHz, CD_3OD-d_4): δ 7.86-7.83 (m, 1H), 7.67-7.65 (m, 1H), 6.87-6.84 (m, 1H), 3.64-3.31 (m, 4H), 3.27-3.12 (m, 1H), 2.14-1.94 (m, 4H). ESI MS *m/z* 297 $[M+H]^+$. Anal. Calcd for $C_{15}H_{16}N_6O \cdot 2HCl \cdot H_2O$: C, 46.52; H, 5.21; N, 21.70. Found: C, 46.73; H, 5.28; N, 21.55.

[00446] Example 29: 4-amino-2-(5-bromo-2-hydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile

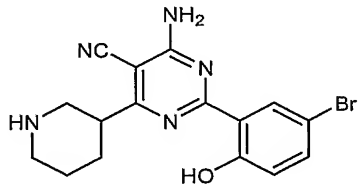
[00447] 

[00448] Step 1: Preparation of 5-bromo-2-hydroxybenzamidine

[00449] 

[00450] To a suspension of NH_4Cl (0.54 g, 10.1 mmol) in toluene cooled to 0°C was added $Al(CH_3)_3$ (2.0 M in toluene, 5.1 mL, 10.2 mmol). After stirring at 0°C for 15 min, the solution was added to a round bottom flask charged with 5-bromo-2-hydroxybenzonitrile (0.50 g, 2.52 mmol). The reaction mixture was heated to 80°C for 14 h. The reaction was cooled to room temperature and poured into a slurry of silica gel (20 g) in $CHCl_3$ (100 mL). The slurry was stirred for 10 min at room temperature, then filtered and washed with a solvent mixture (20% MeOH in CH_2Cl_2) and MeOH until no product eluted out. The filtrate was concentrated to give a light yellow solid. ^1H NMR (300 MHz, DMSO-d_6): δ 10.30 (br s, 1H), 7.76 (d, J = 2.5 Hz, 1H), 7.32-7.21 (m, 4H), 6.61 (d, J = 9.0 Hz, 1H). ESI MS *m/z* 214 $[M]^+$.

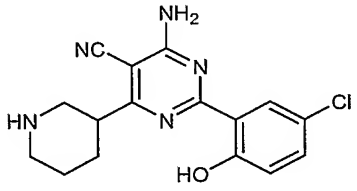
[00451] Step 2: Preparation of 4-amino-2-(5-bromo-2-hydroxyphenyl)-6-piperidin-3-ylpyrimidine-5-carbonitrile

[00452] 

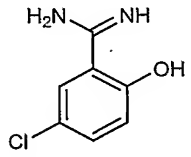
[00453] To a solution of 5-bromo-2-hydroxybenzamidine (Step 1, 0.29 g, 1.38 mmol) in DMF was added NaH (60% in mineral oil, 4 equiv.), and the reaction mixture was stirred for 10 min at room temperature. To the resulting mixture was added tert-butyl 3-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate (**Example 13**, 0.2 g, 0.69 mmol) in DMF and the resulting mixture was stirred for 1 h at room temperature. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl and the product was extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried

(Na_2SO_4) and concentrated. The material was purified by Biotage HPFC. To the yellow solid in a round bottom flask was added 4 N HCl in 1,4-dioxane (5 mL). The mixture was stirred for 45 min at room temperature. The solvent was removed under vacuum and the residue was triturated with MeOH/ether to provide the title compound as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.95 (s, 1H), 9.09 (br s, 1H), 8.85-8.71 (m, 2H), 8.43 (s, 1H), 8.14 (br s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 3.42-3.25 (m, 4H), 3.05-3.02 (m, 1H), 2.03-1.70 (m, 4H). ESI MS m/z 374 $[M+H]^+$. Anal. Calcd for $C_{16}H_{16}BrN_6O \cdot HCl \cdot 0.25H_2O$: C, 46.28; H, 4.25; N, 16.87. Found: C, 46.48; H, 4.02; N, 16.66.

[00454] Example 30: 4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile

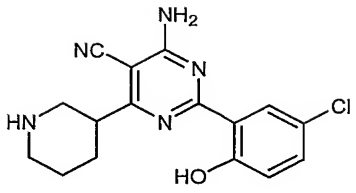
[00455] 

[00456] Step 1: Preparation of 5-chloro-2-hydroxybenzamidine

[00457] 

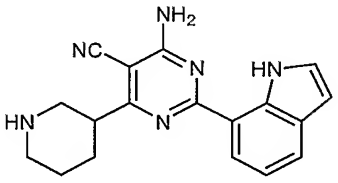
[00458] Prepared as a light yellow solid following a procedure similar to that described in **Example 29, Step 1**, starting with 5-chloro-2-hydroxybenzonitrile (0.5 g, 3.3 mmol). ESI MS m/z 171 $[M+H]^+$.

[00459] Step 2: Preparation of 4-amino-2-(5-chloro-2-hydroxyphenyl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile

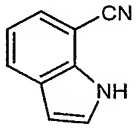
[00460] 

[00461] Prepared as a light yellow solid following a procedure similar to that described in **Example 28, Step 5**, starting with 5-chloro-2-hydroxybenzamidine (Step 1, 0.5 g, 2.9 mmol), but purified by preparative HPLC to give the product as the 0.75 trifluoroacetate salt. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.92 (s, 1H), 9.05 (m, 1H), 8.85-8.71 (m, 2H), 8.31 (s, 1H), 8.15 (br s, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 3.50-3.25 (m, 4H), 3.10-2.97 (m, 1H), 2.03-1.70 (m, 4H). ESI MS m/z 330 $[M+H]^+$. Anal. Calcd for $C_{16}H_{16}ClN_6O \cdot 0.75CF_3CO_2H \cdot 1.25H_2O$: C, 48.01; H, 4.43; N, 16.00. Found: C, 48.19; H, 4.25; N, 15.64.

[00462] Example 31: 4-amino-2-(1H-indol-7-yl)-6-(piperidin-3-yl)pyrimidine-5-carbonitrile

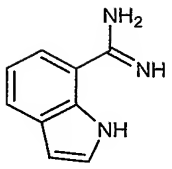
[00463] 

[00464] Step 1: Preparation of 1H-indole-7-carbonitrile

[00465] 

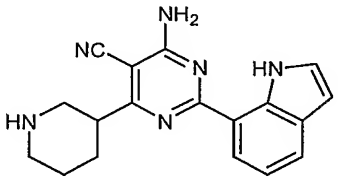
[00466] Prepared as a white solid following a procedure similar to that described in **Example 28, Step 2**, starting with the 7-bromoindole (1.0 g, 5.1 mmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.99 (br s, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.50-7.49 (m, 1H), 7.15 (t, J = 7.7 Hz, 1H), 6.63-6.62 (m, 1H). ESI MS m/z 143 $[M+H]^+$.

[00467] Step 2: Preparation of 1H-indole-7-carboxamidine

[00468] 

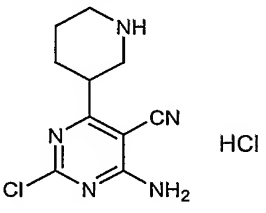
[00469] Prepared as a white solid following a procedure similar to that described in **Example 29, Step 1**, starting with 1H-indole-7-carbonitrile (Step 1, 0.40 g, 2.8 mmol). ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.92 (d, J = 7.9 Hz, 1H), 7.48-7.43 (m, 2H), 7.21 (t, J = 7.7 Hz, 1H), 6.65 (d, J = 3.1 Hz, 1H); ESI MS m/z 160 $[M+H]^+$.

[00470] Step 3: Preparation of 4-amino-2-(1H-indol-7-yl)-6-piperidin-3-ylpyrimidine-5-carbonitrile

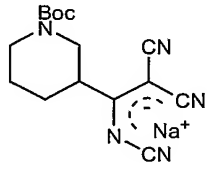
[00471] 

[00472] The above compound was prepared in 9% yield as a brown solid (0.020 g, 0.063 mmol) following a procedure similar to that described in **Example 29, Step 5**, starting with 1H-indole-7-carboxamidine (Step 2, 0.22 g, 1.4 mmol) and tert-butyl 3-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate (**Example 13**, 0.20 g, 0.69 mmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.58 (s, 1H), 8.91 (br s, 1H), 8.67 (br s, 1H), 8.39-8.26 (m, 2H), 7.88-7.72 (m, 2H), 7.50-7.49 (m, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.60-6.59 (m, 1H), 3.49-3.26 (m, 4H), 3.05-3.02 (m, 1H), 2.04-1.77 (m, 4H). ESI MS m/z 319 $[M+H]^+$.

[00473] Example 32: 4-amino-2-chloro-6-(piperidin-3-yl)pyrimidine-5-carbonitrile hydrochloride

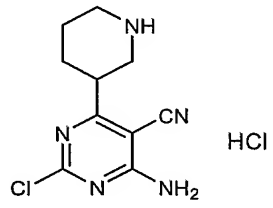
[00474] 

[00475] Step 1: Preparation of 3-cyanamino-2-cyano-3-(1-t-butoxycarbonylpiperidyl)-propenenitrile, sodium salt

[00476] 

[00477] Metallic sodium (0.316 g, 13.74 mmol) was dissolved in EtOH (20 mL) prior to the portionwise addition of cyanamid (0.58 g, 13.73 mmol). The mixture was stirred for 30 min at room temperature, after which time the reaction mixture turned into a white slurry. Tert-butyl 3-(2,2-dicyano-1-methoxyvinyl)piperidine-1-carboxylate (**Example 13**, 4.0 g, 13.7 mmol) was added to the reaction mixture and the resulting mixture was stirred for 1 h. The reaction mixture was concentrated to dryness under reduced pressure and the residue was triturated with $CHCl_3$ to afford a white solid (3.12 g), which was used without further purification in Step 2.

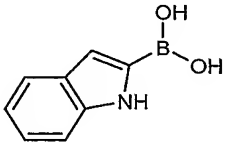
[00478] Step 2: Preparation of 4-amino-2-chloro-6-(piperidin-3-yl)pyrimidine-5-carbonitrile hydrochloride

[00479] 

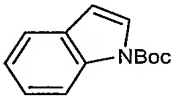
[00480] To a concentrated solution of HCl (13 mL), the solid obtained in Step 1 was added portionwise over 24 min while sporadically cooling the reaction mixture with an ice bath. The mixture thus obtained was stirred at room temperature for 1 h, then diluted with water (100 mL). The precipitate that formed was isolated by filtration. The cake was rinsed with water and dried to afford the title compound as a white solid. mp >300°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.29-9.24 (m, 1H), 9.01-8.93 (m, 1H), 8.63 (br s, 1H), 8.18 (br s, 1H), 3.38-3.30 (m, 2H), 3.28-3.23 (m, 1H), 3.14-3.01 (m, 1H), 2.97-2.76 (m, 1H), 1.96-1.84 (m, 2H), 1.84-1.72 (m, 1H), 1.67-1.57 (m, 1H). ESI MS *m/z* 238

$[M+H]^+$. Anal. Calcd for $C_{10}H_{12}N_5 \cdot HCl$: C, 43.81; H, 4.78; N, 25.55. Found: C, 43.62; H, 4.68; N, 25.19.

[00481] Example 33: 1-(tert-butoxycarbonyl)indolin-2-yl-2-boronic acid

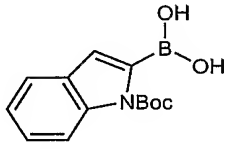
[00482] 

[00483] Step 1: Preparation of tert-butyl 1H-indole-1-carboxylate

[00484] 

[00485] To a solution of indole (3.00 g, 25.6 mmol) in CH_3CN (18 mL) was added di-*tert*-butyl-dicarbonate (6.15 g, 28.2 mmol) and a catalytic amount of DMAP. The solution was stirred overnight at room temperature. The reaction mixture was diluted with cold 1 N HCl (30 mL) and extracted with EtOAc (3 x 30 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was carried forth to the next step.

[00486] Step 2: Preparation of 1-(tert-butoxycarbonyl)indolin-2-yl-2-boronic acid

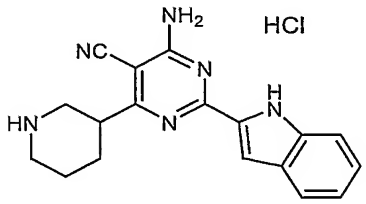
[00487] 

[00488] To an ice-cold solution of tert-butyl 1H-indole-1-carboxylate (Step 1, ~25 mmol) and triisopropyl borate (7.22 g, 38.4 mmol) in THF (32 mL) was added a solution of 2.0 M LDA in THF (16 mL, 32.0 mmol). The reaction mixture was stirred at 0°C for 1 h, after which the reaction was quenched with aqueous 2N HCl (30 mL) and extracted with CH_2Cl_2 (40 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Recrystallization of the residue in 1:1 CH_3CN/H_2O (60 mL) gave the product as

a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.10 (d, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 6.3 Hz, 1H), 7.28-7.17 (m, 2H), 6.63 (s, 1H), 1.68 (s, 9H).

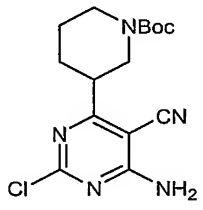
[00489] Example 34: 4-amino-2-(1H-indol-2-yl)-6-piperidin-3-ylpyrimidine-5-carbonitrile hydrochloride

[00490]



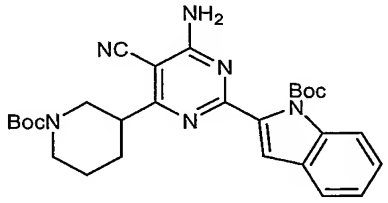
[00491] Step 1: Preparation of tert-butyl 3-(6-amino-2-chloro-5-cyanopyrimidin-4-yl)piperidine-1-carboxylate

[00492]



[00493] To a slurry of 4-amino-2-chloro-6-(piperidin-3-yl)pyrimidine-5-carbonitrile hydrochloride (**Example 32**, 0.50 g, 2.10 mmol) in DMF (10 mL) was added triethylamine (0.9 mL, 6.29 mmol) and di-*tert*-butyl dicarbonate (1.15 g, 5.27 mmol). The reaction mixture was stirred at room temperature overnight, then diluted with EtOAc (100 mL). The solution thus obtained was washed with water (3 x 10 mL), dried (Na_2SO_4) and concentrated to dryness under reduced pressure. The residue was triturated with MeOH to afford the first batch of the desired product as a white solid. The filtrate was concentrated to dryness under reduced pressure. Purification by flash column chromatography (eluent, 1:1 CH_2Cl_2/hexanes to 1:1:1 CH_2Cl_2/hexanes/EtOAc) gave a second batch of the desired product as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (br s, 1H), 8.03 (br s, 1H), 3.98 (br s, 1H), 3.91 (d, *J* = 12.9 Hz, 1H), 3.05-2.76 (m, 4H), 1.93-1.61 (m, 3H), 1.40 (s, 9H).

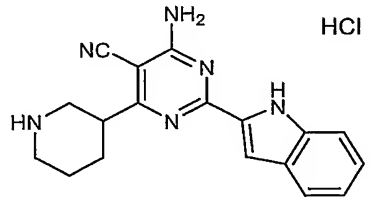
[00494] Step 2: Preparation of tert-butyl 2-{4-amino-6-[1-(tert-butoxycarbonyl)piperidin-3-yl]-5-cyanopyrimidin-2-yl}indoline-1-carboxylate



[00495]

[00496] A dry flask was loaded with tert-butyl 3-(6-amino-2-chloro-5-cyanopyrimidin-4-yl)piperidine-1-carboxylate (Step 1, 0.20 g, 0.59 mmol) and 1-(tert-butoxycarbonyl)indolin-2-yl-2-boronic acid (**Example 33**, 0.30 g, 0.89 mmol). Then was added toluene (7.0 mL) and a 2M aqueous solution of $NaHCO_3$ (2.5 mL). The mixture thus obtained was blanketed with argon and sonicated. $PdCl_2dppf$ (0.039 g, 0.044 mmol) was added and the reaction mixture was heated to 70°C overnight. The cooled reaction mixture was diluted with water (5.0 mL) and the resulting solution was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were concentrated to dryness under reduced pressure. Purification by flash column chromatography (eluent, 1:1 CH_2Cl_2/hexanes to 1:1:1 CH_2Cl_2/hexanes/EtOAc) gave the desired product as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 7.99 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.46-7.38 (m, 1H), 7.33-7.25 (m, 1H), 7.12 (s, 1H), 4.12-3.91 (m, 2H), 3.53-3.45 (m, 1H), 3.12-2.86 (m, 2H), 2.83-2.65 (m, 1H), 1.98-1.85 (m, 1H), 1.83-167 (m, 2H), 1.41 (s, 9H), 1.40 (s, 9H).

[00497] Step 3: Preparation of 4-amino-2-(2,3-dihydro-1H-indol-2-yl)-6-piperidin-3-ylpyrimidine-5-carbonitrile



[00498]

[00499] To a solution of tert-butyl 2-{4-amino-6-[1-(tert-butoxycarbonyl)piperidin-3-yl]-5-cyanopyrimidin-2-yl}indoline-1-carboxylate

(Step 2, 0.20 g, 0.38 mmol) in MeOH (4.0 mL) was added dropwise a solution of 4N HCl in 1,4-dioxane (3.0 mL). The reaction solution was stirred for 4 h at room temperature, then concentrated to dryness under reduced pressure. The residue was triturated with MeOH to afford the title HCl salt as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.62 (s, 1H), 9.35-9.29 (m, 1H), 8.93-8.87 (m, 1H), 7.85 (br s, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 8.20 Hz, 1H), 7.30-7.19 (m, 2H), 7.05 (t, J = 7.2 Hz, 1H), 3.57-3.29 (m, 4H), 3.02-2.82 (m, 1H), 1.99-1.78 (m, 4H). ESI MS m/z 319 $[M+H]^+$. Anal. Calcd for $C_{18}H_{18}N_6 \cdot 1.5HCl \cdot 1.5H_2O$: C, 54.04; H, 5.67; N, 21.01. Found: C, 54.23; H, 5.39; N, 20.64.

[00500] Step 40: IKK-2 IC_{50} determination

[00501] Materials

[00502] SAM$^{2\ TM}$ 96 Biotin capture plates were from Promega. Anti-FLAG affinity resin, FLAG-peptide, NP-40 (Nonidet P-40), BSA, ATP, ADP, AMP, LPS (*E. coli* serotype 0111:B4), and dithiothreitol were obtained from Sigma Chemicals. Antibodies specific for NEMO (IKK-γ) (FL-419), IKK-1(H-744), IKK-2(H-470) and IκBα(C-21) were purchased from Santa Cruz Biotechnology. Ni-NTA resin was purchased from Qiagen. Peptides were purchased from American Peptide Company. Protease inhibitor cocktail tablets were from Boehringer Mannheim. Sephacryl S-300 column was from Pharmacia LKB Biotechnology. Centriprep-10 concentrators with a molecular weight cutoff of 10 kDa and membranes with molecular weight cut-off of 30 kDa were obtained from Amicon. [γ-^{33}P] ATP (2500 Ci/mmol) and [γ-^{32}P] ATP (6000 Ci/mmol) were purchased from Amersham. The other reagents used were of the highest grade commercially available.

[00503] Cloning and Expression

[00504] cDNAs of human IKK-1 and IKK-2 were amplified by reverse transcriptase-polymerase chain reaction from human placental RNA (Clonetech). hIKK-1 was subcloned into pFastBac HTa (Life Technologies) and

expressed as N-terminal His_6-tagged fusion protein. The hIKK-2 cDNA was amplified using a reverse oligonucleotide primer which incorporated the peptide sequence for a FLAG-epitope tag at the C-terminus of the IKK-2 coding region (DYKDDDDKD). The hIKK-2:FLAG cDNA was subcloned into the baculovirus vector pFastBac. The rhIKK-2 (S177S, E177E) mutant was constructed in the same vector used for wild type rhIKK-2 using a QuikChange™ mutagenesis kit (Stratagene). Viral stocks of each construct were used to infect insect cells grown in 40L suspension culture. The cells were lysed at a time that maximal expression and rhIKK activity were demonstrated. Cell lysates were stored at -80°C until purification of the recombinant proteins was undertaken as described below.

[00505] Enzyme Isolation

[00506] All purification procedures were carried out at 4°C unless otherwise noted. Buffers used are: buffer A: 20 mM Tris-HCl, pH 7.6, containing 50 mM NaCl, 20 mM NaF, 20 mM β-Glycerophosphate, 500 uM sodium orthovanadate, 2.5 mM metabisulfite, 5 mM benzamidine, 1 mM EDTA, 0.5 mM EGTA, 10% glycerol, 1 mM DTT, 1X Complete™ protease inhibitors; buffer B: same as buffer A, except 150 mM NaCl, and buffer C: same as buffer A, except 500 mM NaCl.

[00507] Isolation of rhIKK-1 homodimer

[00508] Cells from an 8-liter fermentation of baculovirus-expressed IKK-1 tagged with His peptide were centrifuged and the cell pellet (MOI 0.1, I=72 h was re-suspended in 100 mL of buffer C. The cells were microfluidized and centrifuged at 100,000 X g for 45 min. The supernatant was collected, imidazole added to the final concentration of 10 mM and incubated with 25 mL of Ni-NTA resin for 2 h. The suspension was poured into a 25 mL column and washed with 250 mL of buffer C and then with 125 mL of 50 mM imidazole in buffer C. rhIKK-1 homodimer was eluted using 300 mM imidazole in buffer C. BSA and NP-40 were added to the enzyme fractions to the final concentration

of 0.1 %. The enzyme was dialyzed against buffer B, aliquoted and stored at -80°C.

[00509] Isolation of rhIKK-2 homodimer

[00510] A 10-liter culture of baculovirus-expressing IKK-2 tagged with FLAG peptide was centrifuged and the cell pellet (MOI=0.1 and I=72 h) was re-suspended in buffer A. These cells were microfluidized, and centrifuged at 100,000 X g for 45 min. Supernatant was passed over a G-25 column equilibrated with Buffer A. Protein peak was collected and incubated with anti-FLAG affinity resin on a rotator overnight in buffer B. The resin was washed in batch with 10-15 bed volumes of buffer C. Washed resin was poured into a column and rhIKK-2 homodimer was eluted using 5 bed volumes of buffer B containing FLAG peptide. 5 mM DTT, 0.1% NP-40 and BSA (concentrated to 0.1% in final amount) was added to the eluted enzyme before concentrating in using an Amicon membrane with a molecular weight cut-off of 30 kDa. Enzyme was aliquoted and stored at -80°C.

[00511] Isolation of rhIKK-1/IKK-2 heterodimer

[00512] The heterodimer enzyme was produced by coinfection in a baculovirus system (FLAG IKK-2/IKK-1 His; MOI=0.1 and I=72 h). Infected cells were centrifuged and the cell pellet (10.0 g) was suspended in 50 mL of buffer A. The protein suspension was microfluidized and centrifuged at 100,000 X g for 45 min. Imidazole was added to the supernatant to a final concentration of 10 mM. The protein was allowed to bind 25 mL of Ni-NTA resin by mixing for 2 h. The protein-resin slurry was poured into a 25 mL column and washed with 250 mL of buffer A containing 10 mM imidazole followed by 125 mL of buffer A containing 50 mM imidazole. Buffer A, containing 300 mM imidazole, was then used to elute the protein. A 75 mL pool was collected and NP-40 was added to a final concentration of 0.1%. The protein solution was then dialyzed against buffer B. The dialyzed heterodimer enzyme was then allowed to bind to 25 mL of anti-FLAG M2 agarose affinity

gel overnight with constant mixing. The protein-resin slurry was then centrifuged for 5 min at 2,000 rpm. The supernatant was collected and the resin re-suspended in 100 mL of buffer C containing 0.1% NP-40. The resin was washed with 375 mL of buffer C containing 0.1 % NP-40. The protein-resin was poured into a 25 mL column and the enzyme eluted using buffer B containing FLAG peptide. Enzyme fractions (100 mL) were collected and concentrated to 20 mL using an Amicon membrane with molecular weight cut-off of 30 kDa. Bovine serum albumin was added to the concentrated enzyme to final concentration of 0.1 %. The enzyme was then aliquoted and stored at -80°C.

[00513] Cell Culture

[00514] The wild type (wt) human pre-B cell line, 70Z/3, and its mutant, 1.3E2, were generously provided by Dr. Carol Sibley. Wt 70Z/3 and 1.3E2 cells were grown in RPMI 1640 (Gibco) supplemented with 7 % defined bovine serum (Hyclone) and 50 μM 2-mercaptoethanol. Human monocytic leukemia THP-1 cells, obtained from ATCC, were cultured in RPMI 1640 supplemented with 10% defined bovine serum, 10 mM HEPES, 1.0 mM sodium pyruvate and 50 μM 2-mercaptoethanol. For experiments, cells were plated in 6 well plates at $1x10^6$ cells/mL in fresh media. Pre-B cells were stimulated by the addition of 10 μg/mL LPS for varying lengths of time ranging from 0-4 h. THP-1 cells were stimulated by the addition of 1 μg/mL LPS for 45 minutes. Cells were pelleted, washed with cold 50 mM sodium phosphate buffer, pH 7.4 containing 0.15 M NaCl and lysed at 4°C in 20 mM Hepes buffer, pH 7.6 containing 50 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM sodium orthovanadate, 10 mM β-glycerophosphate, 1 mM NaF, 1 mM PMSF, 1 mM DTT and 0.5 % NP40 (lysis buffer). The cytosolic fractions obtained following centrifugation at 10,000 X g were stored at -80°C until used.

[00515] Immunoprecipitation and Western Blotting

[00516] SF9 cells paste containing rhIKKs were centrifuged (100,000 X g, 10 min) to remove debris. rhIKKs were immunoprecipitated (100 µg of cell paste) from the cell supernatant using 3 µg of anti-NEMO antibody (FL-419), followed by coupling to protein A sepharose beads. rhIKKs were also immunoprecipitated from affinity chromatography purified protein preparations (1 µg) using anti-FLAG, anti-His or anti-NEMO antibodies (1-4 µg) followed by protein A sepharose coupling. The native, human IKK complex was immunoprecipitated from THP-1 cell homogenates (300 µg/condition) using the anti-NEMO antibody. Immune complexes were pelleted and washed 3 times with 1 mL cold lysis buffer. Immunoprecipitated rhIKKs were chromatographed by SDS-PAGE (8% Tris-glycine) and transferred to nitrocellulose membranes (Novex) and detected by chemiluminescense (SuperSignal) using specific anti-IKK antibodies (IKK-2 H-470, IKK-1 H-744). Native IKK-2, IκBα, and NEMO proteins from cytosolic lysates (20-80 µg) were separated by SDS-PAGE and visualized by chemiluminescense using specific antibodies.

[00517] Phosphatase Treatment

[00518] Immunoprecipitated rhIKKs were washed 2 times in 50 mM Tris-HCl, pH 8.2 containing 0.1 mM EDTA, 1 mM DTT, 1 mM PMSF and 2 mM $MnCl_2$ and resuspended in 50 µL. Phosphatase (λPPase, 1000 U) was pre-diluted in the same buffer and added to the IKK samples. Following incubation at room temperature for 30 minutes with intermittent mixing, cold lysis buffer was added to the tubes to stop the reaction. After several washes, 10 % of the beads were removed for Western analysis, and the remaining material was pelleted and resuspended in 100 µL of the buffer used for the *in vitro* kinase assay.

[00519] IKK-1 SAM Enzyme Assay

[00520] IKK-1 kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu), a SAM^{2} ™ 96 Biotin capture plate and a

vacuum system. The standard reaction mixture contained 5 μM biotinylated IκBα peptide, 1 μM [γ-^{33}P] ATP (about 1 X 10^5 cpm), 1 mM DTT, 50 mM KCl, 2 mM $MgCl_2$, 2 mM $MnCl_2$, 10 mM NaF, 25 mM Hepes buffer, pH. 7.6 and enzyme solution (1-10 μL) in a final volume of 50 μL. After incubation at 25°C for 30 min, 25 μL of the reaction mixture was withdrawn and added to a SAM^2 ™ 96 Biotin capture 96-well plate. Each well was then washed successively with 800 μL 2 M NaCl, 1.2 mL of NaCl containing 1% H_3PO_4, 400 μL H_2O, and 200 μL 95% ethanol. The plate was allowed to dry in a hood at 25°C for 1 h and then 25 μL of scintillation fluid (Microscint 20) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard). Under each assay condition, the degree of phosphorylation of IκBα peptide substrate was linear with time and concentration for all purified enzymes. Results from the biotinylated peptide assay were confirmed by SDS-PAGE analysis of kinase reaction utilizing a GST-IκBα$_{1-54}$ and [γ-^{32}P] ATP. The resulting radiolabeled substrate was quantitated by Phosphoimager (Molecular Dynamics). An ion exchange resin assay was also employed using [γ-^{33}P] ATP and GST-IκBα$_{1-54}$ fusion protein as the substrates. Each assay system yielded consistent results in regard to K_m and specific activities for each of the purified kinase isoforms. One unit of enzyme activity was defined as the amount required to catalyze the transfer of 1 nmole of phosphate from ATP to IκBα peptide per min. Specific activity was expressed as units per mg of protein. For experiments related to K_m determination of purified enzymes, various concentrations of ATP or IκBα peptide were used in the assay at either a fixed IκBα or ATP concentration. For IκBα peptide K_m, assays were carried out with 0.1 μg of enzyme, 5 μM ATP and IκBα peptide from 0.5 to 20μM. For ATP K_m, assays were carried out with 0.1 μg of enzyme, 10 μM IκBα peptide and ATP from 0.1 to 10μM. For K_m determination of rhIKK-1 homodimer, due to its low activity and higher K_m for IκBα peptide, rhIKK-1 homodimer (0.3 μg) was assayed with 125 μM IκBα peptide and a 5-fold higher specific activity of ATP

(from 0.1 to 10 μM) for ATP K_m experiments and a 5-fold higher specific activity of 5 μM ATP and IκBα peptide (from 5 to 200 μM) for IκBα peptide K_m experiments.

[00521] IKK heterodimer Resin Enzyme Assay

[00522] IKK heterodimer kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu) (American Peptide Co.). 20 μL of the standard reaction mixture contained 5 μM biotinylated IκBα peptide, 0.1 μCi/reaction [γ-^{33}P] ATP (Amersham) (about 1 X 10^5 cpm), 1 μM ATP (Sigma), 1 mM DTT (Sigma), 2 mM $MgCl_2$ (Sigma), 2 mM $MnCl_2$ (Sigma), 10 mM NaF (Sigma), 25 mM Hepes (Sigma) buffer, pH 7.6 and 20 μL enzyme solution and 10 μl inhibitor in a final volume of 50 μL. After incubation at 25°C for 30 min, 150 μL resin (Dowex anion-exchange resin AG1X8 200-400 mesh) in 900 mM formate, pH 3.0 was added to each well to stop the reaction. Resin was allowed to settle for 1 h and 50 μL of supernatant was removed to a Micolite-2 flat bottom plate (Dynex). 150 μL of scintillation fluid (Microscint 40) (Packard) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard).

[00523] IKK-2 Resin Enzyme Assay

[00524] IKK-2 kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu) (American Peptide Co.). 20 μL of the standard reaction mixture contained 5 μM biotinylated IκBα peptide, 0.1 μCi/reaction [γ-^{33}P] ATP (Amersham) (about 1 X 10^5 cpm), 1 μM ATP (Sigma), 1 mM DTT (Sigma), 2 mM $MgCl_2$ (Sigma), 2 mM $MnCl_2$ (Sigma), 10 mM NaF (Sigma), 25 mM Hepes (Sigma) buffer, pH 7.6 and 20 μL enzyme solution and 10 μL inhibitor in a final volume of 50 μL. After incubation at 25°C for 30 min, 150 μL resin (Dowex anion-exchange resin AG1X8 200-400 mesh) in 900 mM formate, pH 3.0 was added to each well to stop the reaction. Resin was

allowed to settle for 1 h and 50 µL of supernatant was removed to a Micolite-2 flat bottom plate (Dynex). 150 µL of scintillation fluid (Microscint 40) (Packard) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard).

[00525] IKK-2 IC_{50} values obtained from the assay described above are shown in the table below.

Example No.	IKK-2 IC_{50} (µM)
1	0.438
3	0.701
4	0.633
5	3.97
6	4.78
7	>20
8	24.4
9	0.316
10	1.52
11	3.03
12	16.7
18	> 20
19	> 20
20	> 20

Example No.	IKK-2 IC_{50} (µM)
21	> 20
22	> 20
23	7.52
24	13.7
25	3.05
26	> 20
27	> 20
28	> 20
29	0.439
30	0.324
31	> 20
32	> 20
34	> 20